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THE DIFFERENTIATION OF MYELOBLASTS FROM LYMPHOBLASTS BY THEIR MANNER OF LOCOMOTION

A Motion Picture Study of the Cells of Normal Bone Marrow and Lymph Nodes, and of Leukemic Blood

ARNOLD R. RICH, MAXWELL M. WINTROBE AND MARGARET R. LEWIS

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Submitted for publication July 27, 1939

There has long been a divergence of opinion as to the identity or non-identity of the large, immature cells with basophilic, non-granular cytoplasm which are found in the bone marrow and in the lymphoid tissues, and from which, in these respective situations, the granulocytes and the lymphocytes develop. The adherents of the "unitarian," or "monophyletic," interpretation of blood formation regard all of these cells, whether found in the marrow or in the lymphoid tissue, as belonging to one single cell type which they term the "hemocytoblast," and which they believe has the power of producing lymphocytes or granulocytes, depending upon the environmental stimulus. The "dualistic" school, on the other hand, believes that the immature, non-granular forerunners of the polymorphonuclear leucocytes in the marrow are quite different in their potentialities from the similarly appearing forerunners of the lymphocytes in the lymphoid tissues. The former they term "myeloblasts," and believe them to be capable of producing only the granulocytes; the latter they term "lymphoblasts," and regard as being able to produce only lymphocytes.

The difficulty of distinguishing myeloblasts from lymphoblasts on morphological grounds has been the most important factor in the perpetuation of this controversy. The dualists believe that there are certain criteria, relating chiefly to slight differences in nuclear structure, which help to differentiate the non-granular, immature cells of

the marrow from those of the lymphoid tissues. However, even most of the dualists admit that "the differentiation is difficult, and often conclusions must be presumptive rather than final" (1). For the word "difficult" the unitarians would substitute "impossible," for they maintain that the supposed morphological differences between lymphoblasts and myeloblasts are artificial, inconstant, and of no significance as true criteria of differentiation (2). Certainly, among those who are continually faced with the necessity of having to attempt to identify "blast" cells in the blood or tissues in disease, there must be few, indeed, who are not well aware of the fallibility of depending upon the suggested morphological criteria of differentiation.

During a study of the pathogenesis and significance of the acute splenic tumor of infection (3) (4), certain considerations made it desirable to attempt to determine definitely the identity of the large, non-granular, basophilic cells which appear in the spleen in this condition. Acute splenic tumor provides, in itself, an illustration of the lack of dependability of the criteria which are supposed to distinguish lymphoblasts from myeloblasts, for the morphological study of the specific cells of acute splenic tumor has resulted only in a controversy as to their identity. Some investigators have regarded them as lymphoblasts (5); others as myeloblasts (6); and still others as histiocytes (14). Since we, ourselves, were unable to reach any satisfying decision as to their identity by a study of their morphological characteristics, it occurred to us that it might be possible to gain more conclusive information by a study of their vital activities. It is now well recognized that certain different types of motile cells exhibit characteristic and consistent differences in their manner of locomotion (7). The type of locomotion of lymphoblasts and of myeloblasts had, however, not been previously determined, and we therefore undertook the present study in order to learn whether or not these cells exhibit any constant differences in activity which could serve as identifying and differentiating criteria. The application of this study to the problem of the nature of acute splenic tumor is discussed in another place (11). Here, we wish to present only the differences between the vital activities of lymphoblasts and myeloblasts which

this study has brought to light, for these differences provide a new type of evidence against the unitarian view that lymphoblasts and myeloblasts are identical cells.

METHOD

The activity of the cells was studied in tissue cultures by means of motion pictures. Under aseptic precautions small pieces of marrow, lymph node, or buffy coat of centrifugalized blood are cut up in Locke's solution, and a fragment about a millimeter in diameter is placed upon a sterile cover glass and is covered with a small drop of heparinized plasma obtained by adding 0.2 c.c. of a 1:1000 solution of heparin to 10 c.c. of freshly drawn blood. The coverglass is then inverted and sealed over the well of a hollow-ground slide by means of a ring of vaseline. The preparation is placed in an incubator kept at 38°. The contact of the cells with the heparinized plasma causes the latter to clot, and soon the motile cells begin to wander out from the explant into the clot. When migration is well under way the actively moving cells are photographed with a motion picture camera attached to the eye piece of a microscope which is kept in a 37° warm-box. The pictures are taken at a slow rate of speed, (12 per minute), and when projected on the screen the movement of the cells is speeded up about 40 times. This enables one to observe the activity of the cells to great advantage, as it magnifies not only the size but also the rapidity of movement of the cells, and so brings out very clearly the differences in the manner of locomotion of the different cell types. The cells of leukemic blood were obtained by transferring the freshly drawn blood from the syringe into a paraffined tube containing heparin, in the proportion of 0.2 c.c. of heparin (1:1000) to 10 c.c. of blood. After centrifugalization, the buffy coat was transferred to Locke's solution, and small bits were planted at once in tissue cultures as described above.

RESULTS

The type of motion of the myeloblast from normal marrow and from leukemic blood. In order to obtain myeloblasts for study we made use of tissue cultures of the bone marrow of normal rabbits, and of

the marrow obtained by sternal puncture from human beings with normal blood picture; and also of the blood from human cases of myeloid leukemia.

In the cultures of marrow, of course, a variety of cells migrate out from the explant. The *myelocytes* and *polymorphonuclears* can be readily identified by their granules and, in the case of the latter cells, by the shape of the nucleus. The polymorphonuclears are highly active cells. They do not maintain a fixed anterior and posterior end, but may throw out pseudopodia from any side of their body, and frequently and abruptly change the direction of their locomotion, so that they appear in the motion pictures to be continually darting first in one direction and then in another. The movement of the older myelocytes resembles that of the polymorphonuclears (Figs. 36, 37, 38). The very young myelocytes, i.e., those with only a few granules, exhibit a type of locomotion in which the worm-like characteristics of the myeloblast, to be described below, are still evident. With the increase in granules the tendency to throw out pseudopodia from all sides, and to lose the polarity of the myeloblast, becomes steadily more pronounced.

The *mononuclear phagocytes* can be easily recognized by their appearance during locomotion. These cells, whether obtained from the tissues ("histiocytes") or from the buffy coat of centrifugalized blood ("monocytes"), exhibit during motion a characteristic which was described by W. H. Lewis (7). They throw out pseudopodia continually in all directions from all sides of their body and, as in the case of the polymorphonuclear, their line of motion tends to change frequently and abruptly; but the characteristic feature of these cells is that their pseudopodia, which are larger and broader than those of the polymorphonuclears, are bordered by a broad, filmy, ruffle-like margin which undulates continually (Figs. 3 and 15). When these cells become enlarged as a result of phagocytosis they retain their characteristic undulating pseudopodia but tend to migrate less actively.

Megalokaryocytes also wander out from the marrow explants. Their size renders their identification easy. They move slowly, and preserve an elongated, rather cylindrical shape when in motion, though they may bend their bodies in various directions. A small fringe of pseudopodia is seen at the anterior end only (Fig. 16).

In addition to the above-mentioned cells in the zone of migration of bone marrow cultures, there are numerous fairly large cells with clear, non-granular cytoplasm, and with large nuclei in which one or more nucleoli can be seen. These we have interpreted as *myeloblasts*, and this interpretation has been supported by a comparison of these cells with the circulating myeloblasts of myeloblastic leukemia, as we shall see in a moment.

The *myeloblasts* of the marrow exhibit in the moving pictures a peculiar and characteristic type of locomotion. When in motion they have very much the appearance of a rather short angleworm. They assume an elongated, cylindrical form, and move in a twisting, writhing manner which makes it difficult to keep the entire cell in focus for any length of time (Figs. 1, 4, 5, 6, 7, 8). They exhibit a polarity, in the sense of maintaining for considerable periods of time an anterior and a posterior end during locomotion, in contrast, for example, to the monocyte which continually changes its line of motion in the direction of any new pseudopod that may be thrown out from any side of its body. Pseudopodia are present only at the anterior end of the myeloblast, where a small, actively moving fringe is seen. Occasionally, however, these cells suddenly reverse their direction of motion completely. This is sometimes initiated by an abrupt and swift movement of the nucleus backward toward the posterior end of the cell; then a fringe of short pseudopodia appears at what was previously the tail end, and as the cell starts off in the reverse direction the pseudopodia that were at the former anterior end disappear.

The writhing, worm-like manner of locomotion of the marrow cells which possessed the structural characteristics of myeloblasts, and which we interpreted as myeloblasts, was quite different from that of any of the other motile cells of normal blood or bone marrow; but in order to gain further evidence regarding the locomotion of the myeloblast we compared the marrow cells in question with the circulating myeloblasts from cases of myeloid leukemia. To this end, we obtained for study motion pictures of the blood cells from a number of cases of myeloid luekemia. The pictures of several of these cases were unsatisfactory, but those from six cases (history nos. U-39514, U-65824, U-67448, U-74500, 119633, 152352) afforded a clear view of the leukemic cells in motion. Study of the motion pictures of

the migrating cells from these cases of myeloid leukemia showed that the "blast" cells resembled precisely in form and locomotion the bone marrow myeloblasts described above (Figs. 9 through 14, and 34). In four of these cases, myelocytes and young polymorphonuclears predominated in the blood, and there was no difficulty in making a diagnosis of myeloid leukemia clinically. In three of these four cases autopsy was performed and the diagnosis was confirmed by finding myelocytes in the infiltrations (autopsy nos. 12295, 15724, 15107). In two cases, cells of the "blast" type predominated in the blood, and the familiar difficulty in reaching a decision clinically regarding the nature of the "blast" cells presented itself. We shall insert here a brief summary of the essential features of these cases:

W. D. (History no. 119,633). Male, 56 years. W. B. C. 91,000, 57 per cent "blast" cells, 17 per cent myelocytes, 7 per cent juvenile neutrophils, 7 per cent segmented neutrophils, 1 per cent eosinophils, 10 per cent lymphocytes, 1 per cent monocytes. There was great difficulty in the identification of the "blast" cells. Their nuclei were usually oval, sometimes irregular in shape, occasionally markedly indented. The margin of the nucleus was very distinct, the chromatin moderately fine and diffusely distributed. Many cells contained 2 to 5 nucleoli. The cytoplasm was moderately basophilic and contained either no granules, or a few, or, in some instances, a moderate number, as well as one or two rod-like structures (Auer bodies ?). These characters suggested myeloblasts, but numerous and large mitochondria visible in the supravital stains suggested lymphoid cells; and the presence of vacuoles and even inclusions in the cytoplasm of the cells suggested the monocytic series. Clinical impression: acute myeloid (?) leukemia. No autopsy.

M. F. (History no. 152,352). Female, 49 years. W. B. C. 80,000, 91 per cent "blast" cells, with moderately fine nuclear chromatin, several nucleoli, few or no granules in the cytoplasm. These cells were thought by some to be myeloblasts, but were regarded as "atypical lymphocytes" by others. Practically all of the remainder of the cells were mature lymphocytes. Clinical impression: Acute myeloid (?) leukemia. *Autopsy* (16344): Myeloid leukemia, with infiltration of bone marrow, spleen, liver, lymph nodes and (to a slight degree) kidneys with immature myeloid cells. Most of the cells were of the "blast" type, but there were numberous myelocytes in the infiltrations.

In both of these cases the motion pictures of the migrating "blast" cells showed that they had the precise form and manner of locomotion exhibited by the bone marrow myeloblasts and by the myeloblasts from myeloid leukemia in which the majority of cells were

myelocytes. The cells in Figs. 9 through 13 are myeloblasts from case W. D. Those in Fig. 34 are from case M. F.

The type of motion of the lymphoblast from normal lymph nodes and from leukemic blood. In order to obtain lymphoblasts for study, cultures were made of the lymph nodes of young rabbits. In such cultures there migrate from the explant histiocytes, small lymphocytes, large lymphocytes, and still larger cells with a clear, non-granular cytoplasm which are quite different in their locomotion from histiocytes or myeloblasts, and which we interpreted as *lymphoblasts*. In the motion pictures, these latter cells present a strikingly uniform and characteristic appearance during their locomotion. Instead of darting first in one direction and then in another, changing shape continually, as does the monocyte (histiocyte), or wriggling forward in a twisting, worm-like manner, as does the myeloblast, the lymphoblast moves forward in a steady, unperturbed manner, maintaining a persistent anterior and posterior end and a rather fixed shape. It is this shape which is the most characteristic feature of the lymphoblast. In motion this cell preserves a rounded contour, has a few small pseudopodia at the anterior margin only, and a rigid, tail-like process projecting in the rear, giving the cell the general outlines of a hand mirror (Figs. 2, 17, 18, 19). Although the cell is much larger than the lymphocyte, in its polarity, and in the maintenance of a fixed, tail-like process during locomotion, the lymphoblast resembles the lymphocyte as described by W. H. Lewis (8), whose observations on the manner of locomotion of the latter cell we have had frequent opportunity to confirm. Figs. 17, 18, 20 and 33 show plainly the resemblance of the lymphocyte to the lymphoblast. As in the case of the myeloid cells, here, too, the older forms of the lymphoid cells tend to change their shape and direction of motion more frequently than do the immature forms.

The resemblance of the contour of the moving large "blast" cells of the lymph nodes to that of known lymphocytes, as shown in the illustration, and their difference from the other motile cells in manner of locomotion, seemed to leave little doubt that the cells were lymphoblasts; but in order to obtain additional evidence the cells were compared with the circulating lymphoid cells from cases of human lymphoid leukemia. Motion pictures, satisfactory for study, were

obtained of the migrating cells of the buffy coat of ten cases of lymphoid leukemia (history nos. U-33977, U-65530, U-65969, U-64675, U-36834, 107880, 168477, H. L. H. 90480, H. L. H. A-2008, Baltimore City Hospitals 12856). Pictures made of several additional cases were unsatisfactory for study. In five of the ten cases the predominating cells were immature. The autopsies performed on three of these five cases are described below. The remaining five cases were instances of typical lymphoid leukemia in which older forms of lymphocytes predominated. The form and manner of locomotion of the lymphoblasts from these ten cases of leukemia, as shown in the motion pictures, resembled precisely that of the large cells of the lymph nodes that we had interpreted as lymphoblasts (Figs. 21 through 31, and 35).

As in the case of the myeloblastic leukemias, some of the cases of lymphoid leukemia in which the cells were predominantly immature presented difficulties in the attempt to reach a decision as to the nature of the "blast" cells from a study of the blood smears alone, as the following summaries indicate:

W. H. (History no. 107880). Male, 18 yrs. W. B. C. 88,000; 84 per cent immature cells suggesting either lymphoblasts or myeloblasts; 15 per cent mature lymphocytes. Some of the immature cells were very large, with relatively fine nuclear chromatin and large nucleoli. Others were smaller, and the nuclear chromatin was coarser. The cytoplasm was basophilic, and in some cases contained a few granules. 97 per cent of the cells were peroxidase negative. Clinical impression: Acute lymphoid (?) leukemia. *Autopsy* (15473): Lymphoid leukemia, with leukemic infiltrations in lymph nodes, spleen, periportal areas of liver, follicles at base of tongue, bone marrow and kidneys. The majority of the infiltrating cells are typical lymphocytes of small and moderate size, but among them are large, immature "blast" cells.

E. L. (History no. U-36834). Female, 13 yrs. W. B. C. 240,000; 65 per cent "blast" cells; 27 per cent young lymphocytes; 4.5 per cent mature lymphocytes. On the whole, the "blasts" were of only moderate size; their nuclear chromatin was coarse; there were 1 or 2 nucleoli; the cytoplasm was basophilic and in some instances contained granules, suggesting early myelocytes. The nuclei of some of the "blast" cells were lobulated, and occasionally the edge of the cytoplasm was serrated, suggesting the monoblast. Clinical impression: Acute lymphoid leukemia. *Autopsy* (14729): Lymphoid leukemia, with leukemic infiltrations in lymph nodes, spleen, periportal areas of liver, bone marrow, thymus, intestines, and other organs. The infiltrating cells are predominantly lymphocytes, with an admixture of lymphoblasts.

V. B. (History no. U-65969). Female, 31 yrs. W. B. C. 65,400; 90 per cent "blast" cells, which were very difficult to classify in smears and supravital stains. By some they were regarded as lymphoblasts; by others as myeloblasts; and the possibility that they were monoblasts occupied a large part of the speculation, for the nuclear chromatin resembled that of the monocyte and the nuclear shape was often quite irregular. There were 1 or 2 nucleoli. The cytoplasm was basophilic, and contained no granules. The peroxidase stain revealed no granules. In supravital stains most of the cells showed a moderate number of neutral red vacuoles. Clinical impression: probably acute monocytic leukemia. *Autopsy* (14536): There was difficulty in making a diagnosis of the type of leukemia. The distribution of the infiltrations was characteristic of lymphoid leukemia, i.e., periportal infiltration of the liver, involvement of the thymus, enlargement of the lymphoid follicles at the base of the tongue, in addition to the involvement of the lymph nodes, spleen, bone marrow, kidneys, etc. However, while it is true that the infiltrations in certain situations (e.g., the periportal areas in the liver) tend to be especially prominent in lymphoid leukemia, this is no absolute criterion; and the irregularity in the shape of the nuclei of the leukemic cells was greater than ordinarily observed in lymphoid cells. It is well recognized, however, that nuclear irregularities, often quite pronounced, may occur in young pathological lymphocytes (see, for example, the pathological lymphoid cells in infectious mononucleosis, Figs. 32 and 33). In none of the infiltrations were definite myeloid cells found. Myelocytes, it will be remembered, are very commonly present in the infiltrations of "monocytic leukemia" (13).

Motion pictures of the predominating migrating "blast" cells in all of the above cases showed that they had the form and manner of locomotion exhibited by the lymphoblasts of normal lymph nodes, and of cases that were unmistakably lymphoid leukemia, both clinically and pathologically. The type cell from case W. H. is illustrated in Figs. 23, 24 and 35; from case E. L., in Fig. 30; from case V. B., in Figs. 25 and 26. In this latter case typical "hand-mirror" lymphoid cells predominated in the cultures during the first day. In cultures that were over 24 hours old numerous monocytes were seen. Monocytes are present in the cultures of most leukemic bloods from the beginning, and it may be noted that an increase in the number of monocytes may occur in tissue cultures after 24 hours as a result of the proliferation of these cells.

The type of motion of the circulating cells in infectious mononucleosis. While there was for a time some doubt as to whether the abnormal large mononuclear cells in the blood in infectious mononucleosis are monocytes or are lymphoid cells, it is generally agreed at the present

time that they are lymphoid (1). We have studied in motion pictures the cells from the blood of a typical case of this disease, and our observations support entirely the current view, for the specific large cells in the blood of the case studied had the shape and manner of locomotion characteristic of the lymphoblast, and were entirely different from the monocyte. The cells shown in Figs. 32 and 33 are examples of the typical cells from the case studied, the essential clinical features of which were the following:

R. K. (History no. 106342). Male, 34 yrs. Chills and fever for 2 weeks. Spleen just palpable. Lymph nodes at angles of jaws enlarged. Slight jaundice. Heterophile antibody, positive 1:2,000. W. B. C. 12,850. 71 per cent lymphoid cells, of which 66 per cent were of the type characteristic of infectious mononucleosis (irregular, slightly lobulated nucleus, non-granular foamy cytoplasm). *Note the lobulated nuclei in the cells in Figs. 32 and 33.*

DISCUSSION

The studies presented here indicate that in spite of the fact that it may be very difficult or impossible to distinguish lymphoblasts from myeloblasts in the lifeless, stained condition, these two types of cells differ decidedly from each other in their living activities. The marked difference in their locomotion, as demonstrated by motion pictures, may be regarded as a new type of evidence against the "unitarian," or "monophyletic," theory of blood formation, which has assumed, on the basis of the appearance of the stained cells, that there is no difference whatever between lymphoblasts and myeloblasts and, therefore, no reason for believing that two different types of "blast" cells exist.

As might be expected, it has not been possible for us to identify with certainty each cell seen in the motion pictures. Some of the unidentified cells may be cells that are abnormal because of trauma; some may be abnormal for other reasons. We have recently observed a case of clinically and histologically typical lymphosarcoma in which the lymphoid tumor cells cultured from a lymph node removed during life, exhibited a type of locomotion that was quite different from that of normal lymphocytes; and the motion pictures of the blood of a case of leukemia of doubtful type showed predominantly "blast" cells with a type of locomotion that, in the single specimen of blood ob-

tained, we were unable to classify. Indeed, considering the fact that leukemia represents, in all probability, a malignant tumor of blood cells, the wonder is that in so many cases the leukemic cells retain the form of locomotion characteristic of their normal cell type. However, regardless of the fact that cells which we are at present unable to identify with certainty are encountered in the motion pictures, the great majority of myeloblasts from normal bone marrow and from the blood in myeloid leukemia have conformed to a definite type of locomotion which is very different from that of the great majority of lymphoblasts from normal lymph nodes and from the blood of cases of lymphoid leukemia. It should furthermore be stated that in six of the cases of leukemia studied we obtained motion pictures of the cells on more than one occasion, and the characteristic activity of the cells from each of these cases remained constant in the motion pictures of the different samples of blood taken from the patient at different times.

The active motility of lymphoblasts and myeloblasts, as shown in the motion pictures, may be surprising to those who have studied these cells from leukemic blood by the usual wet film technique, for under that condition these cells usually remain motionless. Dameshek (12), for example, states that one of the most important criteria in the differentiation of monocytes from myeloblasts is that monocytes display pseudopodia and active movement, whereas myeloblasts exhibit no motion; and Clough (13), noting that certain non-granular cells in a case of leukemia showed pseudopodia, regarded this as "evidence of a degree of motility of which myeloblasts and myelocytes would not be capable." The wet film technique is, however, decidedly unfavorable for the study of the locomotion of certain blood cells. This may be due to the physical forces in play in the capillary film between the slide and the cover glass, or it may possibly be due to damage to the cells produced by the application of the cover glass; but, for whatever cause, the difference between the activity of various cells in the wet film, as contrasted with the hanging drop tissue culture, is very great. As an example, it may be noted that Sabin (9) observed that in wet films the normal large lymphocyte "very seldom shows any locomotion," and that the small lymphocyte, likewise "seldom moves at all." Dameshek (12), also, lists the

lymphocyte as having no motility. There is no question but that these observations are correct in the case of wet film preparations. In hanging drop tissue cultures, however, the lymphocytes can be seen to be extraordinarily active—a fact which becomes impressively evident in the motion pictures. W. H. Lewis (10) has made careful measurements of the rate of locomotion of normal lymphocytes in hanging drop cultures, and has found that many move as fast as polymorphonuclear leucocytes, or even faster. With this we can agree from a study of our films.

Since, in the motion pictures, the shape of the lymphoblast during locomotion has differed so strikingly from that of the migrating myeloblast, the possibility obviously presents itself that this difference may be used as a criterion for diagnostic purposes, and we are at present attempting to perfect a simple and convenient technique that will permit the direct observation of the characteristic locomotion of each type of blood cell.

SUMMARY

In this study, the behavior of lymphoblasts from normal lymph nodes and from the blood of cases of lymphoid leukemia has been compared by means of motion pictures with that of myeloblasts from normal bone marrow and from the blood of cases of myeloid leukemia. The comparison has revealed a striking difference between the manner of locomotion of lymphoblasts and that of myeloblasts. These observations provide a new type of evidence against the "unitarian" interpretation of blood formation which assumes, on the basis of the appearance of the cells in stained preparations, that lymphoblasts and myeloblasts are identical.

The manner of locomotion of the mononuclear phagocyte ("monocyte"; "histiocyte") has conformed to that described for this cell by other observers, and in this study has been found to be entirely different from that of either the lymphoblast or the myeloblast.

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PLATE I

All of the photographs are of living, moving, unstained cells, and were enlarged directly from the negatives of the motion picture films. The cells that are rounded up are cells that were not in motion at the moment.

FIG. 1. Diagram of "worm-like" shape of myeloblast in motion.

FIG. 2. Diagram of "hand-mirror" shape of lymphoblast in motion.

FIG. 3. Diagram of monocyte (histiocyte) in motion.

FIGS. 4, 5, 6, 7. (×1000) Myeloblasts from bone-marrow of normal rabbits.

FIG. 8. (×1000) Myeloblast from normal human bone-marrow.

FIGS. 9, 10, 11, 12, 13. (×1000) Myeloblasts from blood of human acute myeloid leukemia, Case W. D., History No. 119,633, described in text.

FIG. 14. (×1000) Myeloblast from blood of another case of human acute myeloid leukemia, Case W. D., History No. 74,500. W.B.C. 8,800; myeloblasts 1 per cent; undifferentiated myelocytes 5 per cent; differentiated myelocytes 11 per cent; juvenile neutrophils 31 per cent; segmented neutrophils 38 per cent. Acute illness. Clinical impression: Acute myeloid leukemia (aleukemic). Autopsy (15107): Myeloid leukemia, with infiltrations containing myelocytes and myeloblasts in bone-marrow, spleen, liver, lymph nodes, kidneys. Many peroxidase-positive cells.

FIG. 15. (×1000) Two monocytes from normal human blood. Note broad, ruffle-like pseudopodia.

FIG. 16. (×1000) Megalokaryocyte from normal rabbit bone-marrow. Below is a rounded-up polymorphonuclear leukocyte.

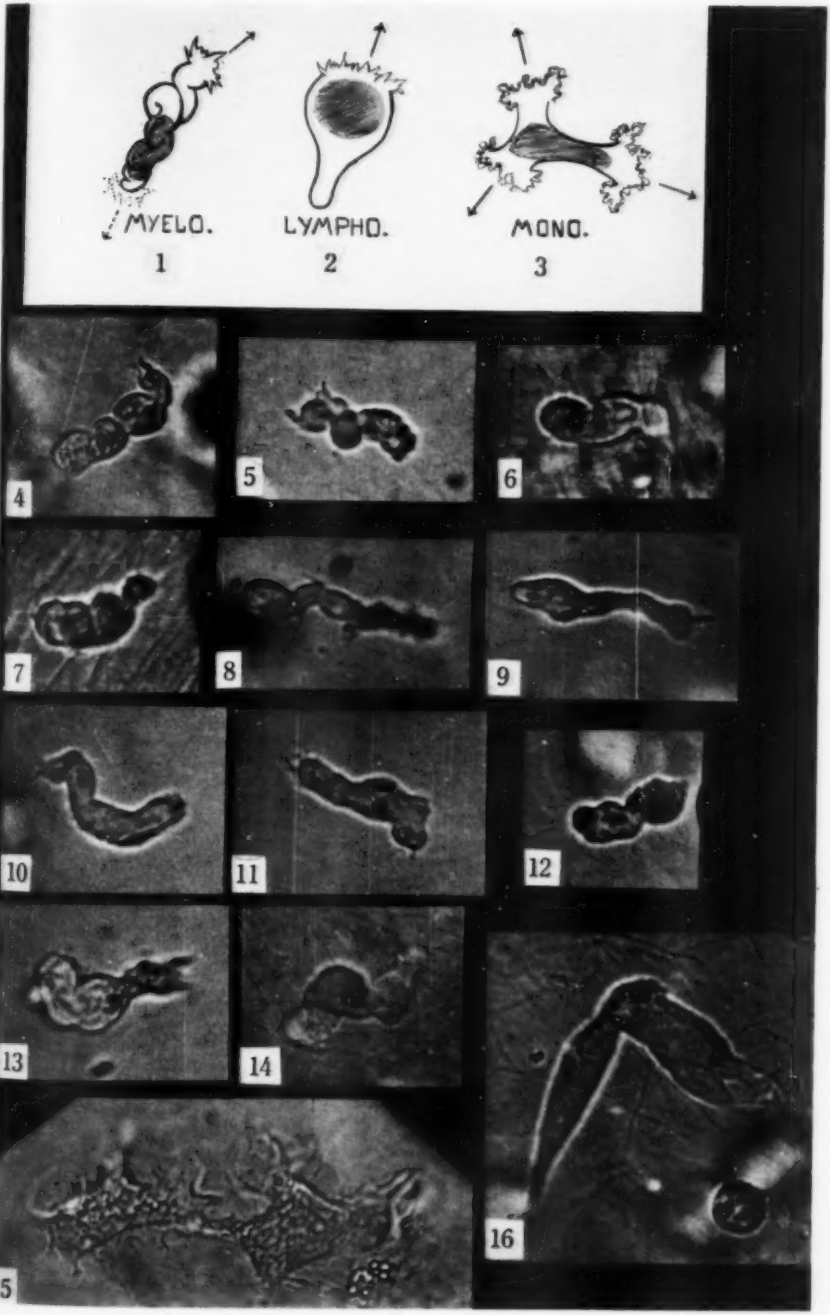
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PLATE II

FIGS. 17, 18, 19. (×1000) Cells from lymph node of 3-weeks-old normal rabbit. There are two moving large lymphoblasts (A) in Fig. 17, two (A) in Fig. 18 and one in Fig. 19. Note the "hand-mirror" shape of the moving small lymphocytes (B) in Figs. 17 and 18 in comparison with that of the lymphoblasts.

FIG. 20. (×1800) Lymphocyte from normal rabbit spleen.

FIGS. 21 and 22. (×1000) Lymphoblasts from blood of human acute lymphoid leukemia (aleukemic state), Case M. P., History No. H. L. H. 90480. W.B.C. 2,300–4,500; lymphoblasts 23 per cent; lymphocytes 66 per cent, monocytes 1 per cent; juvenile and segmented neutrophils 8 per cent; myelocytes 1 per cent.

FIGS. 23 and 24. (×1000) Lymphoblasts from blood of human acute lymphoid leukemia, Case W. H., History No. 107880, described in text. See Fig. 35.

FIGS. 25 and 26. (×1000) Lymphoblasts from blood of human acute lymphoid leukemia, Case V. B., History No. U-65969, described in text.

FIGS. 27, 28, 29. (×1000) Typical cells from blood of human chronic lymphoid leukemia, Case M. L., History No., Balto. City Hosp. 12856. 95 per cent of cells were typical small and moderate size lymphocytes.

FIG. 30. (×1000) Lymphoblast of moderate size from blood of human acute lymphoid leukemia, Case E. L., History No. U-36834, described in text.

FIG. 31. Low power picture showing cells beginning to migrate out from the explant into the clot. Mass of cells at bottom are leucocytes of buffy coat of blood of human acute lymphoid leukemia, Case T. G., History No. U-65530. W.B.C. 81,000; lymphoblasts 91 per cent. Autopsy (14543): Lymphoid leukemia, with infiltrations of small lymphocytes and lymphoblasts in liver, spleen, lymph nodes, bone-marrow, thymus. No oxidase positive cells in infiltrations. *Note the uniformity of the "hand-mirror" contour of the migrating lymphoblasts, to which the arrows point.*

FIGS. 32 and 33. (×1000) Characteristic large lymphoid cells from blood of case of infectious mononucleosis described in text. Note the lobulated nuclei. Fig. 33 shows two small lymphocytes in motion near the large cell.

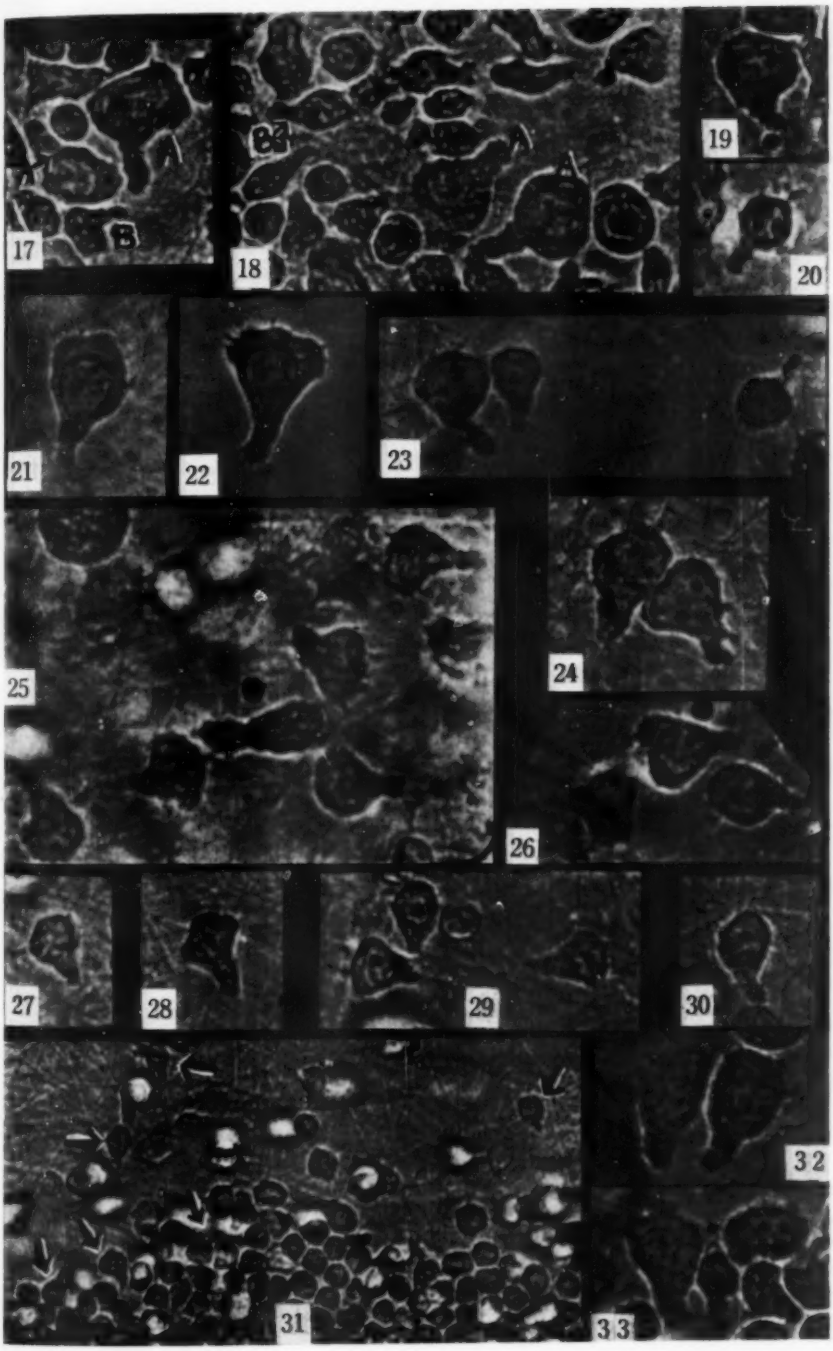
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PLATE III

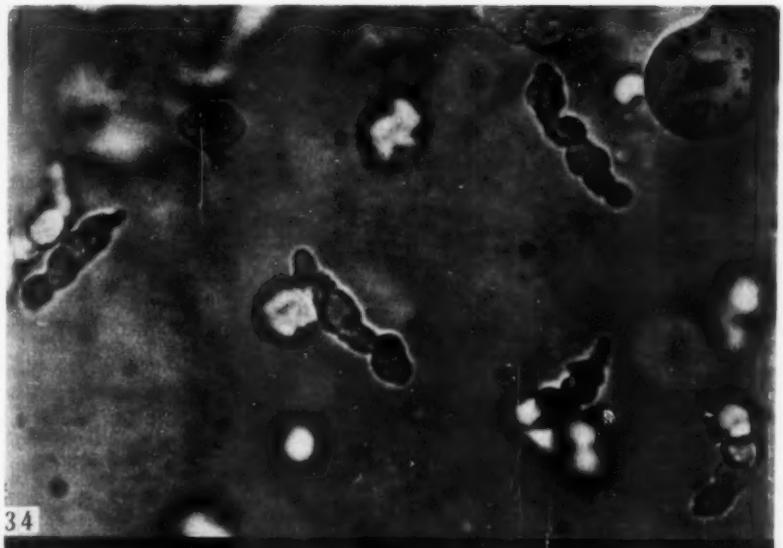
FIG. 34. (×1000) Myeloblasts from blood of human acute myeloid leukemia, Case M. F., History No. 152,352, described in text. Entire field, to show uniformity of "worm-like" shape of moving myeloblasts.

FIG. 35. (×1000) Lymphoblasts and large lymphocytes from blood of human acute lymphoid leukemia, Case W. H., History No. 107,880, described in text. Entire field, to show uniformity of "hand-mirror" shape of lymphoid cells in motion.

FIG. 36. (×1000) Myelocyte from culture of normal human bone-marrow.

FIG. 37. (×1000) Myelocyte from culture of normal rabbit bone-marrow.

FIG. 38. (×1000) Large myelocyte from blood of typical case of human chronic myeloid leukemia, Case I. Mc., History No. U-67448; Autopsy No. 15724.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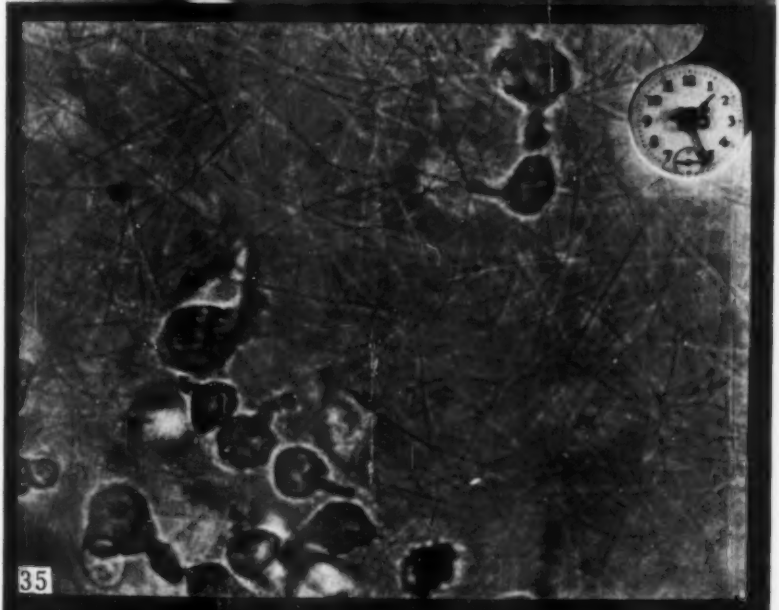
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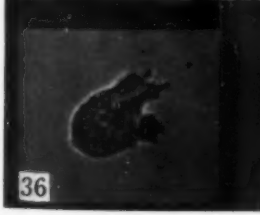
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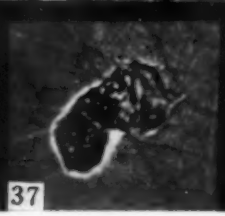
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THE ACTIVITY OF THE LYMPHOCYTE IN THE BODY'S REACTION TO FOREIGN PROTEIN, AS ESTABLISHED BY THE IDENTIFICATION OF THE ACUTE SPLENIC TUMOR CELL*

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It is well known that during infections the spleen commonly becomes enlarged, and that there appear in its pulp great numbers of mononuclear cells. This condition is ordinarily called "acute splenic tumor," and its nature and significance have long been subjects of investigation, speculation and debate.

The most constantly present cells in acute splenic tumor are large mononuclear cells with rounded nuclei and a non-granular, basophilic cytoplasm. Plasma cells may also appear, particularly in infections of longer duration, but they are not always present, whereas the large basophilic cells always are. There are reasons for believing that the plasma cell may be a modified form of the large basophilic cell, but we shall not deal here with the origin and function of the plasma cell. The observations that we shall present will be concerned only with the large basophilic cell which is constantly in evidence in the spleen whenever the condition of acute splenic tumor exists.

What is the nature of these large cells which proliferate to such a marked degree under the stimulus of infection, and what function does this intense cellular activity serve? A great deal of investigation and of speculation have left these questions without a satisfactory answer. Some observers have concluded that the cells are histiocytes (1); others have regarded them as lymphoblasts (2); and still

* Presented in abstract before the Fifty-fourth Session of the Association of American Physicians, Atlantic City, May 3, 1939.

others as myeloblasts (3). The lack of agreement regarding the nature of these cells is not difficult to understand, for they have heretofore been studied only in stained preparations, and there are no staining characteristics which will distinguish with certainty between lymphoblasts, myeloblasts and young histiocytes. Numerous attempts have been made to set up distinguishing criteria, relating chiefly to nuclear structure; but the conflicting views regarding each of the postulated criteria bear witness to the fact that no generally acceptable difference between the morphology of these cells in their dead state has yet been demonstrated to exist (4). Indeed, it has been this very difficulty in detecting any consistent and reliable morphological differences between the various "blast" cells which has led many hematologists to adopt the "unitarian" or "monophyletic" interpretation of blood formation—a view which maintains that lymphoblasts and myeloblasts have an identical structure and are, actually, identical cells, which have the power of producing lymphocytes or granulocytes depending upon the environmental stimulus. In a separate study (5) we have shown that even though lymphoblasts and myeloblasts may be indistinguishable in fixed and stained preparations, in their behavior in the living state they appear to be very different from each other; and it is this recognizable difference in their vital activity that, in the present experiments, we have sought to apply to the answer to the question: "What is the nature of the large mononuclear acute splenic tumor cell?"

Regarding the second question: "What function does the intense cellular proliferation in acute splenic tumor serve?" the answer to this question has been dictated largely by the particular opinion which the individual writer has held regarding the identity of the acute splenic tumor cell. Since the polymorphonuclear leucocyte is known to be important in the phagocytic defense against bacteria, those who regard the acute splenic tumor cells as myeloblasts believe that acute splenic tumor serves the function of producing phagocytic polymorphonuclears to help in the combat against the infecting bacteria (3). Since the histiocytes are widely believed (though without proof) to be able to produce antibodies, it is believed by those who regard the acute splenic tumor cells as histiocytes that the reaction represents a production of histiocytes for the purpose of antibody formation (1).

Since the function of the lymphoid cells is so dark a mystery, most of those who regard the acute splenic tumor cells as lymphoblasts refrain from speculation regarding the function which these cells serve.

The fact that infection with bacteria of widely different types produces the same type of mononuclear cell proliferation in the spleen, as pointed out by MacCallum (6) and others, strongly suggests that the cellular activity in acute splenic tumor represents a response to some one factor that is common to bacterial infections in general. Several years ago, one of us, while engaged in a study of the mechanism of hypersensitivity to foreign proteins, became impressed by the enlargement of the spleen which regularly occurred in the animals that received injections of foreign protein, and reported the results of an investigation into the nature of this phenomenon (7). It was possible to show that when sterile, non-bacterial foreign protein, such as horse serum or egg white, is introduced repeatedly into the body, by whatever parenteral route, there occurs a splenic enlargement, which, if the injections are continued, increases progressively until the spleen is really enormous (Fig. 1). Microscopically, it was found that during the first 24 to 48 hours following the first injection of foreign protein a marked degree of mitotic activity begins in the Malpighian bodies, and there appear large, basophilic mononuclear cells which are identical in appearance with those in the acute splenic tumor produced by bacterial infection (Figs. 4 and 5). If the injections of protein are continued, these cells increase greatly in number and spread out into the pulp, until the microscopic picture is precisely that of the acute splenic tumor of infection (Fig. 2). Plasma cells also make their appearance in the spleen under these conditions.

A search of the literature showed that a proliferation of large mononuclear cells in the spleen had been observed by several investigators following the injection of foreign non-bacterial protein for various purposes; but the resemblance of the proliferating cells to those in acute splenic tumor was not noted by any of those investigators, nor was there any agreement between their interpretations as to the nature of the proliferating cells. Epstein (8) regarded them as histiocytes; Kuczynski (9) and Wiseman (10) as young lymphoid cells; and Apitz (11) as "primitive mesenchymal cells."

The reproduction of the complete picture of acute splenic tumor in

our experiments with sterile, non-bacterial foreign proteins (7) made it clear for the first time that bacterial infection is not at all necessary for the occurrence of this condition. Nothing peculiar to bacteria or their products, or to the state of infection, is required to bring about the development of a typical acute splenic tumor. The presence in the tissues of sterile foreign protein, whether bacterial or non-bacterial in origin, is all that is necessary to incite this reaction. There can be little doubt that the enlargement of the spleen that is recognized clinically during serum sickness represents, in the human being, the counterpart of the acute splenic tumor that we have produced in our animals by the injection of foreign serum.

The identification of the acute splenic tumor cell. A study of the tissues of the experimental animals killed at various intervals after the injection of foreign protein showed that this mononuclear-cell proliferation in the spleen was the earliest recognizable morphological reaction to the protein. This fact, together with the possible implications in regard to the problem as to what cells are responsible for antibody formation, made it desirable to attempt to determine more precisely the nature of the specific proliferating cells. Since previous attempts to identify these cells on morphological grounds has led only to contradictory opinions, and since we, ourselves, were unable to reach any decision as to their identity by that means, we turned to the study of the cells in their living state. It was shown a decade ago by W. H. Lewis (12) and others that certain types of motile cells exhibit characteristic and consistent differences in their manner of locomotion. It seemed of moment, therefore, to undertake a study of the manner of locomotion of the acute splenic tumor cell, with a view toward comparing its locomotion with that of myeloblasts, lymphoblasts and histiocytes. The manner of locomotion of the histiocyte had been well established by the previous studies of Lewis (12) and others, but the type of locomotion of myeloblasts and lymphoblasts had not been determined, and it was necessary to learn whether these cells could be distinguished from each other by their locomotion, before the problem of the nature of the acute splenic tumor cell could be attacked by this method. We therefore undertook to study the manner of locomotion of myeloblasts and of lymphoblasts by means of motion pictures of their activity in tissue cultures. The results of this study (5) showed

that the lymphoblast exhibits a type of locomotion that is quite different from that of the myeloblast, and that the locomotion of both of these cells is different from that of the histiocyte. These differences, as described and abundantly illustrated in our preceding paper (5), are as follows:

The mononuclear phagocytes of the tissues ("histiocytes") and those of the circulating blood ("monocytes") have an identical type of locomotion. They throw out large pseudopodia continually in all directions, from all sides of their body; their line of motion tends to change frequently and abruptly, so that they appear in the motion pictures to be continually darting first in one direction and then in another; and, finally, their pseudopodia are bordered by a broad, filmy, ruffle-like margin which undulates continually, and which constitutes the most characteristic feature of these cells (Fig. 10). When these cells become enlarged as a result of phagocytosis they retain their undulating pseudopodia but tend to migrate less actively.

The myeloblasts have a peculiar, worm-like type of locomotion. They assume an elongated, cylindrical form, and move in a twisting, writhing manner which makes it difficult to keep their entire body in focus for any length of time (Figs. 7, 8, 9). They exhibit polarity, in the sense of maintaining for considerable periods of time an anterior and a posterior end during locomotion, in contrast to the histiocyte (monocyte) which continually changes its line of motion in the direction of any new pseudopod that may be thrown out from any side of its body. Pseudopodia are present only at the anterior end of the myeloblast, where a small, actively moving fringe is seen. Occasionally, however, these cells suddenly reverse their direction of motion completely. At such times a fringe of little pseudopodia appear at what was previously the tail end, and as the cell starts off in the reverse direction the pseudopodia that were at the former anterior end disappear.

The lymphoblasts exhibit in motion pictures a strikingly characteristic form, and type of locomotion. Instead of darting first in one direction and then in another, changing their shape continually, as do the histiocytes (monocytes), or wriggling forward in a twisting, worm-like manner, as do the myeloblasts, the lymphoblasts move forward in a steady, unperturbed manner, maintaining a persistent anterior and posterior end and a rather fixed shape. It is this shape which is the most characteristc feature of the lymphoblast. In motion this cell preserves a rounded contour, has a very narrow fringe of pseudopodia at the anterior margin only, and a rigid, tail-like process projecting in the rear, giving the cell the general outlines of a hand-mirror (Figs. 11 through 16).

In order to compare the large basophilic mononuclear cell of acute splenic tumor with the lymphoblast, myeloblast and histiocyte, motion pictures were made of tissue cultures of normal spleens and of spleens

that were in the condition of acute splenic tumor. The technique employed is described in our previous paper (5) and need not be repeated here.

In the cultures of the acute splenic tumor spleens produced by the intravenous injection of foreign protein into rabbits many of the specific large cells migrate out from the explant and are strikingly evident from their size, which surpasses that of the other cells of the spleen. Occasional cells of this type are encountered in the normal spleen, but in acute splenic tumor their number is so greatly increased that they are abundant in smears and in the cultures.

In our first study of the acute splenic tumor cell several years ago (13) we determined that it is quite different from the histiocyte in the fundamental fact that it is not phagocytic. The histiocytes of the spleen and the monocytes of the blood avidly ingest foreign particulate matter. This can be readily demonstrated *in vitro* by placing particles, such as carbon or carmine, in wet films or tissue cultures containing these cells; and the *in vivo* phagocytic activity of these cells in the spleen can be readily demonstrated by studying scrapings or sections of the spleen following the injection of foreign particles into the circulation. Under these *in vitro* and *in vivo* conditions we found that the acute splenic tumor cells remained indifferent to the presence of the particulate matter. We have never observed any of the foreign particles in their cytoplasm, whereas adjacent histiocytes (monocytes) showed active phagocytosis.

The acute splenic tumor cell differs from the histiocyte not only in its absence of phagocytic activity, but also in its type of locomotion. In our early studies of the vital activity of these cells we were impressed by the resemblance of their type of motion to that of lymphocytes, but the activity of the lymphoblasts and myeloblasts had not then been determined, and for that purpose it was necessary to obtain motion pictures of the cells from cases of lymphoid and myeloid leukemia as well as from normal bone marrow and lymph nodes. It has required several years for the accumulation of a sufficient number of properly studied cases of leukemia, which, together with our studies of the cells of normal lymph nodes and bone marrow, have established the differentiation of lymphoblasts, myeloblasts and histiocytes (monocytes) by their manner of locomotion as described above. Com-

parison of the motion pictures of the acute splenic tumor cells with those of the lymphoblasts, myeloblasts and histiocytes shows that in form and locomotion the acute splenic tumor cell is entirely different from the histiocyte (monocyte) and the myeloblast, and is precisely like that of the lymphoblast from normal lymph nodes and from the blood of cases of lymphoid leukemia (Figs. 17 through 25). These differences and similarities are illustrated in the accompanying prints made from the motion picture films.

DISCUSSION

The studies that we have described here demonstrate, in the first place, that infection is not necessary for the occurrence of acute splenic tumor. This condition represents a reaction of the body to foreign protein, whether bacterial or non-bacterial in origin.

In the second place, by means of a criterion (the type of locomotion) which we believe to be more reliable in the differentiation of lymphoblasts from myeloblasts than are the controversial staining reactions, the present studies identify the specific, proliferating large basophilic cells of acute splenic tumor as being lymphoid in character. While these cells resemble lymphoblasts in all observed respects, we would not insist that they necessarily are lymphoblasts in the sense of being immature lymphoid cells. It is conceivable that they may be lymphocytes which are greatly enlarged because they are performing some special function. One may recall in this connection the great enlargement of the monocytes into macrophages under special conditions of functional activity. The basophilic protoplasm, however, suggests immaturity.

Since these studies identify the acute splenic tumor cells with the lymphoid cells, it is of interest to state that precisely the same type of cellular proliferation as that observed in acute splenic tumor can be shown to occur in lymph nodes that drain infected tissues. The lymph nodes that drain a pneumonic lung, for example, often show in a brilliant manner a great proliferation of typical "acute splenic tumor cells"; and we have observed the same reaction in lymph nodes draining the sites into which foreign protein was injected in experimental animals. Wiseman (10), also, has noted proliferation of large basophilic cells in lymph nodes following the parenteral injection

of foreign protein and Ehrich (14) observed the same type of reaction in the lymph nodes draining sites infected with staphylococci in experimental animals. It was Wiseman's opinion, from their staining reactions, that the large cells were lymphoid. In Ehrich's opinion they were reticulo-endothelial. We have made no motion pictures of these cells, but direct observation has shown that they have the type of locomotion characteristic of the lymphoblast. This lymphoid cellular proliferation is, doubtless, responsible in part at least for the enlargement of the lymph nodes that drain infected sites in the human being; for the lymph node enlargement that occurs during the "serum sickness" that results from foreign protein injections in man; and for the swelling of the lymph nodes that Longcope (15) described long ago in animals into which he had injected foreign protein.

What, finally, can we conclude regarding the function of this lymphoid cellular activity that occurs as a response to foreign protein? The lymphocyte has long been a cell of mystery. In spite of the enormous numbers of these cells that are present in the body, they have successfully eluded all attempts to fathom their functional significance. They have been said, though without proof, to play a rôle in fat metabolism; in digestion; in "detoxification"; in protection against cancer; and as the forerunner of all forms of blood cells. In addition, it was suggested long ago by Kuczynski (21), and more recently by Wiseman (10), that the lymphocytes are concerned in some way with the handling of foreign protein that enters the tissues undigested. This suggestion was made on the basis of the morphological interpretation of the proliferating cells as being lymphoid in character. As pointed out above, however, others on the basis of morphology, interpreted the cells as being myeloid (3), reticulo-endothelial (8), or primitive mesenchymal cells (11). The present studies provide a new type of evidence that the cells which proliferate so strikingly in the presence of foreign protein are lymphoid; and since these cells respond so promptly and in so specific a manner to the parenteral presence of foreign protein, it is tempting to suspect that they may be concerned in some way in the process of antibody formation. This has been suggested from time to time, but has been ignored by most writers, who prefer to regard the histiocytes as the probable producers of antibody. The latter view is, undoubtedly,

an appealing one, if only for the reason that the histiocytes ingest foreign colloids so avidly, as shown by their phagocytosis of colloidal dyes. It has seemed reasonable to believe that the cells which take all kinds of foreign colloids into their body may be the cells which manufacture the antibodies against foreign proteins. There is, however, no actual evidence that the histiocytes produce antibody. Attempts have been made to interfere with antibody formation by overloading the histiocytes with various phagocytizable materials (the so-called "blockade of the reticulo-endothelial system"), but the results have been highly conflicting (22), and even when positive are subject to a variety of interpretations. The facts that antibody formation can be depressed by splenectomy, and that during immunization antibody can be demonstrated in the spleen and regional lymph nodes earlier or in higher concentration than in other tissues, have often been advanced as evidence that the histiocytes, which are particularly abundant in the spleen and lymph nodes, manufacture the antibody; but this argument would obviously apply equally well to the lymphocyte, for there are many more lymphocytes than histiocytes in these organs.

There are, indeed, a number of facts which render the possibility that the lymphocyte may play a rôle in antibody formation worthy at least of consideration and study. Certainly, the lymphoid hyperplasia in the spleen described in this paper is the earliest morphological response that we have been able to detect in the body following the intravenous injection of foreign proteins that incite antibody formation. This lymphoid activity can be demonstrated within 24 hours after the injection of the protein, and it is well developed before any change in the number or appearance of the histiocytes can be detected. We have been unable to produce the reaction by the injection of serum from the same species, or of carbohydrates that do not incite antibody formation (e.g., repeated injections of a 50 per cent glucose solution, and of a non-antigenic polysaccharide derived from the pneumococcus). Furthermore, it is suggestive that the infant is decidedly deficient in the ability to produce antibodies (16) (17) (18), and one of us has pointed out that, in parallel fashion, acute splenic tumor rarely becomes so well developed during infections in infants as in older children or adults (19). It is also interest-

ing that in animals raised from birth in a strictly bacteria-free environment, the most striking deviation from the "normal" is a marked inconspicuousnes of the lymphoid tissue of the entire body (20). Other suggestive observations come to mind, such as the tendency for lymphocytoses to occur during convalescence from infections. The possible rôle of the lymphoid cells in the process of antibody formation requires, however, much more study before we shall be able to speak with any confidence about it one way or the other. At present, we can say only that one function of the lymphoid cell is concerned in some way with the body's response to the presence of foreign protein in the tissues. This fact creates at least a definite breach in the wall of complete mystery that has so long surrounded the function of the lymphoid cell, and with the guiding knowledge that the lymphocytes are concerned in some way with the body's reaction to foreign protein, there is promise that more definite information as to their precise activity in this direction may be forthcoming.

SUMMARY

1. Infection is not necessary for the occurrence of acute splenic tumor. This condition represents a reaction to the parenteral presence of foreign protein, whether bacterial or non-bacterial.

2. Lymphoblasts, myeloblasts and histiocytes (monocytes) can be distinguished from each other by their type of locomotion. Motion picture study of the large, basophilic, mononuclear acute splenic tumor cells in comparison with lymphoblasts, myeloblasts and histiocytes (monocytes) shows that the type of locomotion of the acute splenic tumor cell is precisely like that of the lymphoblast, and quite different from that of the myeloblast or the histiocyte (monocyte). It is therefore concluded that the large basophilic mononuclear cells which proliferate in the spleen in acute splenic tumor are lymphoid in character.

3. Lymph nodes draining infected tissues or a site into which foreign protein has been injected, exhibit a lymphoid cell proliferation entirely like that characteristic of acute splenic tumor.

4. Since the present studies identify as lymphoid the cells which proliferate so promptly following the parenteral injection of foreign protein, it is concluded that one function of the lymphocyte is concerned in some way with the body's reaction to foreign protein.

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PLATE I

FIG. 1. "A" shows enlargement of spleen of rabbit produced by repeated injections of foreign protein. This rabbit (No. 9) received 12 intravenous injections of sterile horse serum in 1 to 5 cc. amounts at intervals during a period of one month. "B" is spleen of rabbit of same weight that received control injections of normal saline.

FIG. 2. Typical acute splenic tumor produced in rabbit (No. 37) by injection of 2 cc. sterile horse serum every other day for a month. Note the dense infiltration of the pulp with mononuclear cells, in comparison with Fig. 3. No infection at autopsy.

FIG. 3. Spleen of normal rabbit for comparison with Fig. 2.

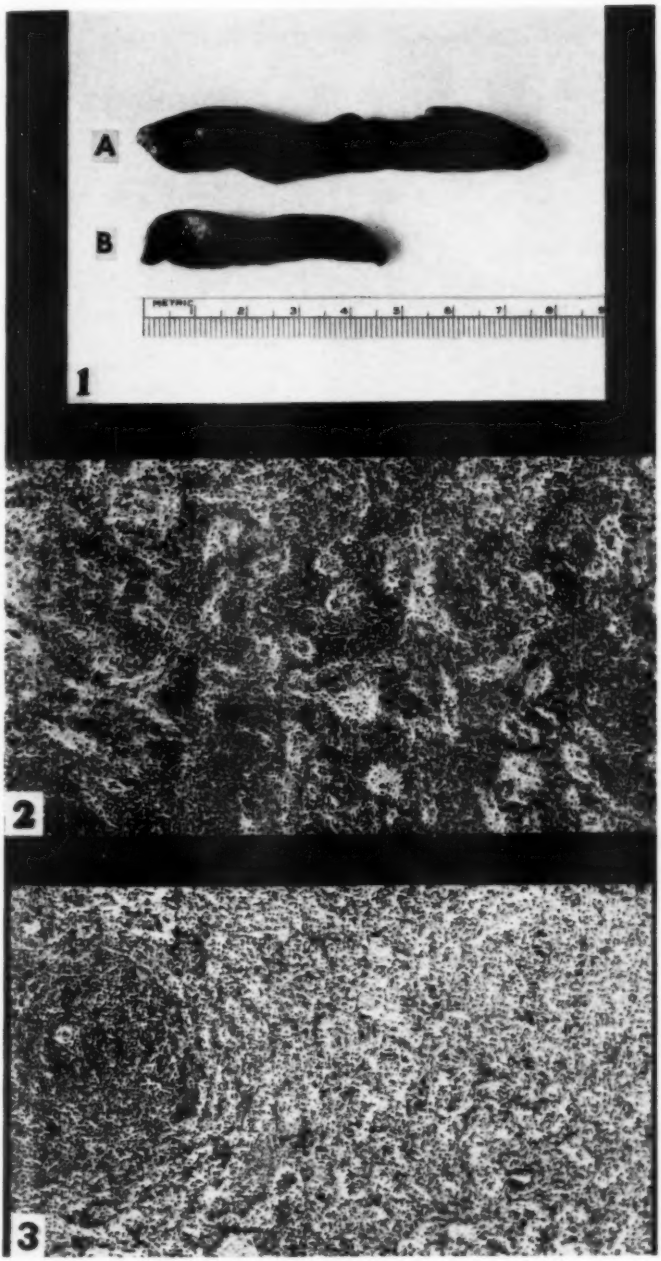
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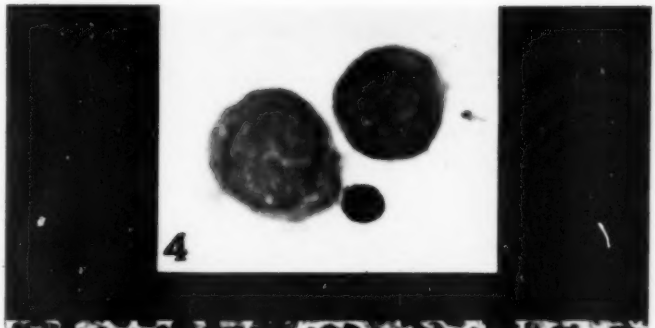
PLATE II

FIG. 4. Two acute splenic tumor cells (lymphoblasts) from smear of spleen of rabbit (No. 35) that had received 5 cc. of sterile horse serum intravenously and was killed 72 hours later. A small lymphocyte is near one of the lymphoblasts. Wright's stain.

FIG. 5. Edge of Malpighian body of spleen of rabbit (No. 26) that had received 5 cc. sterile horse serum intravenously and was killed 72 hours later. Note the many large lymphoblasts in comparison with the cells in Fig. 6. Arrow points to mitosis.

FIG. 6. Edge of Malpighian body of normal rabbit spleen, showing uniformity of size of small lymphocytes in contrast to the cells in Fig. 5.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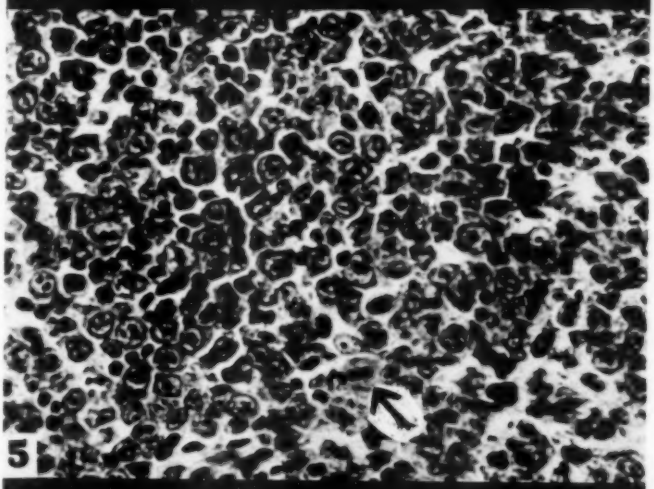
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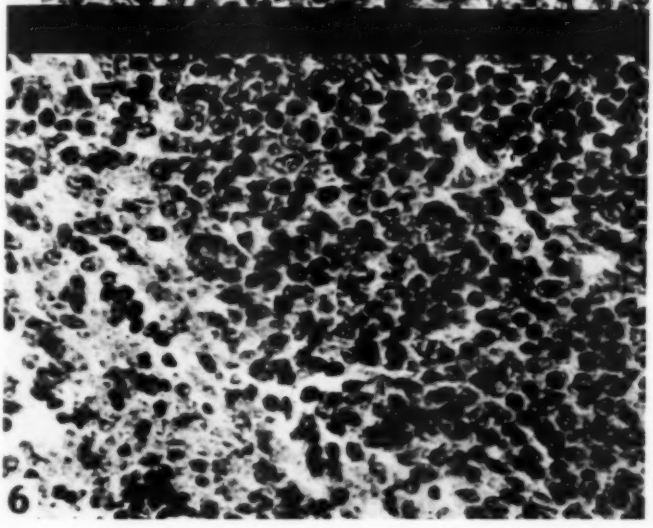
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PLATE III

(Figs. 7 through 25 are photographs of living, moving, unstained cells, enlarged from the negatives of the motion picture films.)

FIG. 7. (×1000) Myeloblast from bone marrow of normal rabbit. Note "worm-like" shape.

FIG. 8. (×1000) Myeloblast from blood of human acute myeloid leukemia. Case M. F., history No. 152,352, described in reference 5.

FIG. 9. (×1000) Myeloblast from blood of human acute myeloid leukemia. Case W. D., history No. 119,633, described in reference 5.

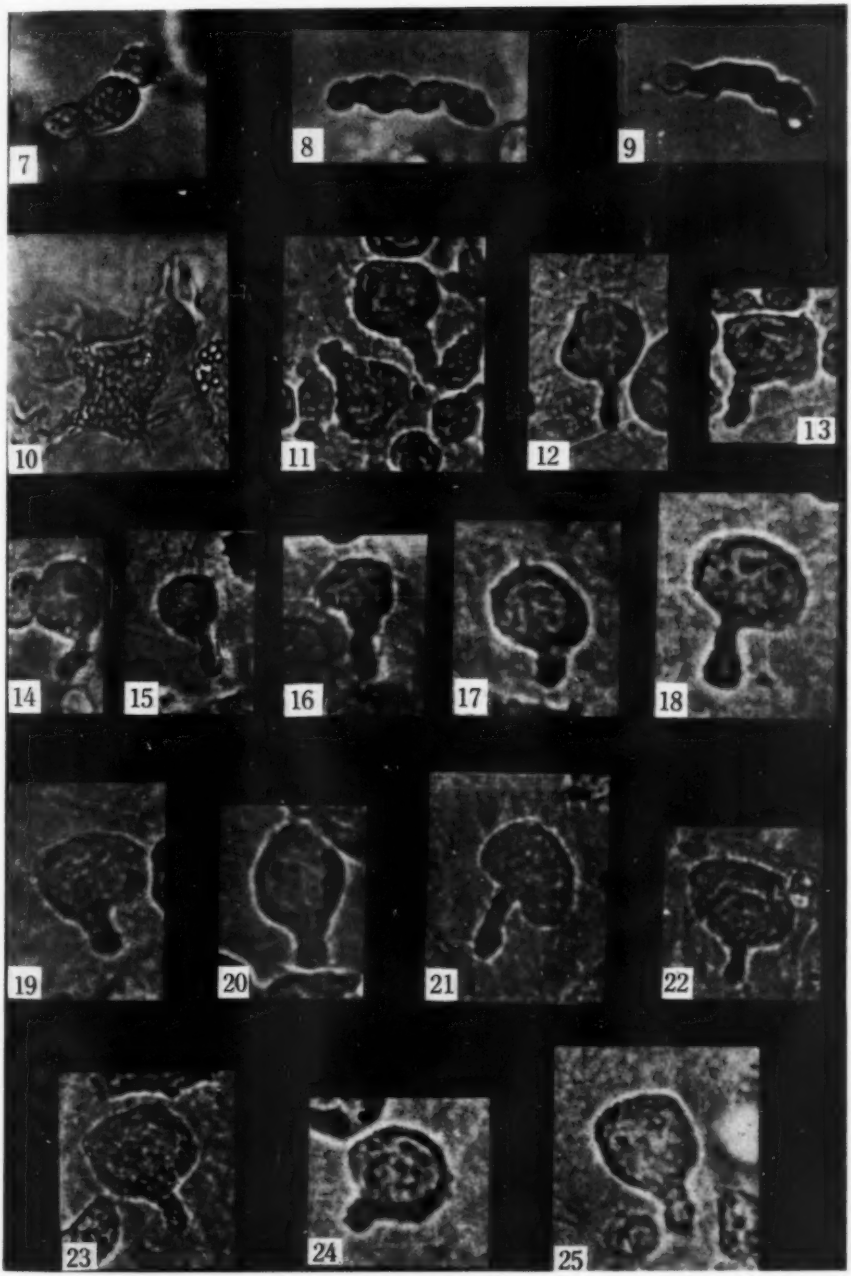
FIG 10. (×1000) Monocyte from normal human blood. Note broad, ruffle-like pseudopodia.

FIGS. 11, 12, 13. (×1000) Lymphoblasts from lymph node of 3 weeks old rabbit. Note "hand-mirror" shape.

FIGS. 14 and 15. (×1000) Lymphoblast and large lymphocyte from blood of human acute lymphoid leukemia. Case W. H., history No. 107,880, described in reference 5.

FIG. 16. (×1000) Lymphoblast from blood of human acute lymphoid leukemia. Case V. B., history No. U-65969, described in reference 5.

FIGS. 17 through 25. (×1000) Acute splenic tumor cells of rabbit No. 45, that received 5 cc. sterile horse serum intravenously and was killed 72 hours later. Note identity of appearance with that of the lymphoid cells in Figs. 11–16, and difference from myeloblast (Figs. 7, 8, 9) and monocyte (Fig. 10). In the normal spleen these large lymphoid cells are rare.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TRANSIENT PARALYSIS FROM POSTURAL HYPOTENSION

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In tracing the development of the term apoplexy Thomas (1), writing in Osler's System of Medicine, showed that it originally meant "to strike off or be disabled by a stroke." Chaucer and Shakespeare so use it and Thomson in his "Castle of Indolence" (1748) has the following:

> "The sleepless Gout here counts the crowing cocks,
> A wolf now gnaws him, now a serpent stings;
> Whilst Apoplexy cramm'd Intemperance knocks
> Down to the ground at once, as butcher felleth ox."

Later apoplexy referred only to hemorrhage and was even used to describe bleeding from the kidney as "renal apoplexy." "At the present time," Thomas said, "the best English usage is reverting to the original meaning, although the word even yet bears with it a distinct idea of hemorrhage."

Many of the early writers mentioned paralysis of brief duration and Marshall Hall's (2) Croonian Lectures in 1851 dealt with "The Threatenings of Apoplexy and Paralysis. . . ." He thought, as had Cullen and Abercrombie (3), that venous congestion was the cause of paroxysmal attacks of apoplexy. He described transient hemiplegia associated with epilepsy and attributed it to venous congestion caused by contractions of the muscles of the neck.

Todd (4) in 1854 published a series of Clinical Lectures on Paralysis. He thought that congestion produced by an epileptic attack might lead to rupture of blood vessels but not to paroxysmal attacks of apoplexy. He says "The erect posture, for example, is favourable to these attacks, and they are sometimes relieved by the assumption of the horizontal position, or by hanging down the head. A patient here, two or three years ago, was seized with attacks of this kind

whenever he sat up in bed." Stokes in his book on Diseases of the Heart and Aorta—Dublin, 1853, describes the case of a patient who awakened in the morning with hemiplegia and jaundice both of which would clear up promptly under stimulants—the hemiplegia in a few hours and the jaundice by the next day. This was a case of mitral insufficiency with extreme dilatation. Another of Stokes patients "learned to ward off such attacks by placing himself on his hands and knees with his head dependent." It is probable that Adams in his description of cardiac syncope described two such cases.

Leonard Hill's (5) (1896) classical monograph presented evidence which gained wide acceptance at the time, in favor of the concept that the cerebral vessels possess little or no vaso-motor control and respond only passively to the systemic venous and arterial pressures. However, a number of case reports by clinicians in the first decade of the 20th century reporting transient paralysis, hypothecated arterial spasm in the brain. In fact, George Peabody (6) advanced this theory in 1891 to explain the transient attacks in a number of his cases in which post mortem examination revealed extensive arteriosclerosis of the cerebral vessels but no local lesion such as hemorrhage, softening, or oedema. Osler (7) (1911) accepted this view as the most plausible one and reported several cases, one that of his old teacher and friend, Dr. George Ross, which is so typical that it bears repeating. "My introduction to this condition occurred under peculiar circumstances: As a young man in Montreal there were two doors I never passed,—47 and 49 Union Avenue; going up I called on Dr. Palmer Howard, and if he was not in or was engaged I called on Dr. George Ross; going down, the reverse. One morning I had a shock, the first of the kind I had ever felt—I realized that my dear friend George Ross was seriously ill. He had always seemed well and strong, though one hot day, in 1878, at the old Savile Club in London, he had an attack of shortness of breath. This day he told a strange story: he had been awakened by the night bell, and, attempting to put out the right hand to get the match-box he found he had lost power in it. With his left hand he struck a match and rang the bell. When the servant came he could not speak. He realized perfectly what had happened—that he had had a stroke; but to his surprise in a few hours power had returned to his arm, and he could

speak, but not quite clearly. When I saw him he was quite himself—no trace of paralysis, and the speech was clear. Arteries like whip-cord—apex beat out—the usual story that we now know so well. This was the first of a series of transient attacks of aphasia, monoplegia, and hemiplegia extending over four or five years, with intervals of good health during which he lectured and carried on his practice. Once on his return from Europe with Dr. Roddick and Dr. Alloway he had an attack of partial paraplegia and had to be helped off the steamer, but it disappeared in the course of a couple of days."

Osler says, "The mode of origin of these cerebral crises in arteriosclerosis has been much discussed of late years by William Russell in his work on Arterial Hypertonus, etc., (1907), by Edgeworth, Parker, Langwill and Heard, Allan, and others." "We have plenty of evidence that arteries may pass into a state of spasm with obliteration of the lumen and loss of function in the parts supplied. In the peripheral arteries in Raynaud's disease we can sometimes feel the spastic, cord-like vessel; in the retina we can sometimes see the arteries contracted. Both in Raynaud's disease and in the remarkable thrombo-angiitis described by Buerger the obliteration may persist until necrosis occurs, but in many instances it is only transient and the circulation is restored. A case of Raynaud's disease, with recurring attacks of aphasia, hemiplegia, and loss of consciousness, some occurring coincidentally with the local asphyxia and necrosis, convinced me that intermittent closing of the cerebral vessels could occur, and the transient nature of the attacks with complete recovery seems to offer no other explanation so satisfactory. And we know now that there are neither anatomical nor physiological objections to this view as applied to the cerebral arteries."

Forbes (8) and his co-workers have in recent years brought forth conclusive evidence of the contractility of the small vessels on the surface of the brain in laboratory animals, and Cushing (9) and other brain surgeons have made important observations during the course of operations on the human brain. These facts do suggest the possibility of spasm of cerebral vessels but do not indicate the part it plays in transient paralysis.

In 1911 Fleming and Naffziger (10) reviewed the subject of transient paralysis and concluded that, in patients with sclerosed and narrowed

cerebral vessels lowering the blood pressure below an essential minimal level would produce symptoms which would disappear if the blood pressure rose again soon enough. As possible causes of a sudden fall in blood pressure they mentioned myocardial weakness, surgical shock, and dilatation of the splanchnic vessels occurring during a meal.

For some years I have observed two cases of transient aphasia and paralysis. Both patients are elderly individuals with advanced arteriosclerosis and one has a life long history of migraine headaches. In the latter case the attacks of paralysis are frequently preceded by what the patient calls blind spots and what I take to be scotomata. A third case came under my care last year. A man of 65 years suddenly fell to the ground and was unable to get up for some minutes on account of weakness of one leg. Ten minutes later the strength returned completely to his leg. While being studied in the hospital he was observed in several spontaneous attacks and we were able to precipitate others.

In view of the knowledge now at hand in regard to cases of so called postural hypotension and also in regard to reflex regulation of the blood pressure by the carotid sinus, I wish to report the findings in this case of transient paralysis and to discuss the treatment indicated.

Case History: (# 140,262). This 65 year old white male entered the Johns Hopkins Hospital on May 6th, 1938, with the chief complaint of periodic attacks of numbness and weakness of the right side of the body for the past two weeks.

Family History: Mother died at 61 years of cancer of breast. Father died at 59 years of diabetes and "stroke." One brother died at 45 of nephritis. No family history of tuberculosis. Patient's daughter has asthma. Married 33 years. Wife living and well.

Past History: General health always very good. Usual childhood diseases. Scarlet fever during childhood. No other serious infectious diseases. As a boy he suffered Colle's fracture of right wrist with deformity. Eyes: Used glasses for 25 years; occasional amblyopia in left eye. No diplopia. Ears: Slight impairment of hearing in left ear. No earache or tinnitus. Nose: Frequent head colds, especially during the winter. Chronic sinusitis for 6–7 years. No epistaxis. Heart: No precordial pain, palpitation, orthopnea or oedema. Some dyspnoea on exertion. Gastro-intestinal: Ten years ago patient began to have dull epigastric pain relieved by taking food. X-rays at this time revealed no ulcer, although his doctor kept him on soft diet for about a year. When he returned to normal diet, there was recurrence of the pain. Bowels regular. Stools normal. Hemorrhoidectomy 15 years ago. Genito-urinary: Nocturia

occasionally. No frequency, hematuria, or difficulty in starting stream. Weight: Average 170 lbs. plus. Weighed over 180 lbs. a year ago. Habits: Led quite an active life until 3 years ago. Has been very sedentary since that time. Smokes 20 cigarettes daily. Alcohol occasionally. Occupation: Retired financier. Takes almost no exercise and reads constantly. Personality: Intelligent, pleasant, alert and cooperative.

Present Illness: The patient was apparently in good health until two weeks ago when he suddenly experienced numbness and weakness in the right leg. He was walking at the time and fell to the floor before he could catch himself. The numbness and weakness were limited to the right leg, lasted about 10 minutes, and disappeared entirely without any residual symptoms. That same night he became dizzy and fell in the bathroom but got up immediately. No numbness or weakness noted at this time. Attacks similar to the first one recurred a week later and again yesterday and the last attack was followed by temporary loss of use of the right arm.

He has had intermittent dull occipital headaches for the past 3 months. No nausea or vomiting.

At the time of admission he was not able to write the order for his dinner but about an hour later could write quite freely.

Physical Examination: Temperature: 98.6. Pulse: 88. Respirations: 20. Blood Pressure: 150/84.

The patient is a well developed and well nourished 65-year-old male who looks worried and tired but is in no apparent distress.

Skin: Warm, moist and elastic. No petechiae or eruptions. Mucous membranes of good color. *Lymph nodes:* No general enlargement. *Upper extremities:* Deformity of right wrist due to old Colle's fracture. No clubbing or cyanosis of digits. *Head:* Normal contour. No sinus or mastoid tenderness. *Eyes:* Conjunctivae, corneae and sclerae clear. Extraocular movements well performed. No nystagmus. Pupils equal, regular and react actively to light and during accommodation. Ophthalmoscopic: Discs well outlined. Increased narrowing and tortuosity of retinal arteries with arterio-venous compression. No hemorrhage or exudate. *Ears:* No gross hearing defects. *Nose:* Nasal septum intact. Ample breathing space. *Mouth:* Lips moist, with fissures. Many teeth missing. Partial upper and lower dental plates. Remaining teeth in good condition. Tongue is coated. Buccal surfaces clean. *Pharynx:* Not injected. *Neck:* Thyroid not enlarged. No nodules. Trachea is in the midline. *Spine:* Somewhat stiff. *Chest:* Symmetrical. Expansion is equal on the two sides. Percussion note hyperresonant throughout. At both bases dry, sibilant rales are heard on both inspiration and expiration. Descent of lungs equal but limited. *Heart:* Precordium quiet. No thrusts or thrills. Apex impulse palpable. Heart not enlarged. Left border of dulness 9.5 cm. Retro-manubrial dulness not increased. Rhythm regular. Vessel walls thickened. *Abdomen:* Rounded; relaxed musculature. No tenderness or palpable masses. Liver at costal margin. Spleen

not felt. *Genitalia:* No abnormalities. *Lower extremities:* No oedema or varicose veins. Good pulsation of dorsalis pedis arteries. *Neurological:* Cranial nerves all intact. No incoordination. *Reflexes:* Ankle jerks and knee jerks present bilaterally but definitely exaggerated on the right. No clonus. Biceps and triceps equal bilaterally. Babinski negative. *Rectal:* Prostate diffusely enlarged, not tender; no stony hard areas.

Laboratory Findings: Blood counts: Red blood cells: 5,580,000. Hemoglobin: 17.3 gm. or 119 per cent. Volume packed red blood cells: 50.0. White blood cells: 9,250. Sedimentation rate: 12.0 mm. in one hour (corrected: 16.0 mm.). Differential: juvenile neutrophiles 1 per cent, segmented neutrophiles 77 per cent, eosinophiles 1 per cent, lymphocytes 20 per cent, monocytes 1 per cent. *Wassermann reaction:* negative. *Stool:* Brown, semi-solid. No gross blood or mucous. Benzidine: 2 plus. *Urine:* Slightly cloudy, straw-colored. Specific gravity 1.012. Acid. Sugar and albumin: 0. Phosphate crystals 2 plus. Microscopic: Occasional white blood cells. No red blood cells or casts. Blood Chemistry: Nonprotein nitrogen 29 mgm. per 100 cc. Sugar 85 mgm. per 100 cc. Calcium 10.3 mgm. per 100 cc. Phosphorus 3.3 mgm. per 100 cc. Protein 7.1 gm. per 100 cc. (refractive index). *Phthalein test:* Total 2 hour output 75 per cent. *Basal metabolic rate:* plus 1 per cent. Test satisfactory. *Fluoroscopic examination:* The stomach is normal in size and tone. It is moderately prolapsed and functions normally. No evidence of an organic lesion in either the stomach or duodenum. *X-ray report:* Chest: Marked emphysema. Lungs clear. Heart and aorta normal in size. Head: Sella turcica is normal. A linear area of calcification is seen lateral to and on a level with the sella turcica. It is in the position of the internal carotid artery and the calcification could well be within the walls of the vessel. (Dr. J. L. Pierson). *Electrocardiogram:* (Analysis of record taken in Washington by Doctor Worth Daniels) Rate: 75. Rhythm: sinoauricular. Interval: 0.16. QRS duration normal. Diagnosis: Normal sinus rhythm. T I inverted. T II and III upright. The chest lead lacks an initial downward Q and has an upright T. The record shows definite evidence of myocardial damage.

Progress note: About 8.00 A.M. on the morning of May 8th the patient experienced gradual onset of weakness of right arm; there was almost complete loss of function. No involvement of lower extremity at this time. Neurological examination was essentially negative except for flaccid paralysis of right arm with hyperactive reflexes. Attack subsided in about 45 minutes. About 20 minutes later the same episode repeated itself, this time involving both the right upper and right lower extremities and presenting the same neurological findings as before, except for a positive Babinski reflex on the right. Blood pressure during first attack was 138/80; during second attack, 115/70.

On account of the drop noted during these attacks the blood pressure was recorded with the patient lying, sitting and standing, and it was found that there was a consistent fall when the patient stood up.

Observations were made by Dr. L. W. Eichna with the patient on a mechanical tilting table (May 11, 1938. Room temperature 22.0°–22.5°C.):

TIME	REMARKS AND BLOOD PRESSURE	PULSE
3:16	Patient arrived in wheel chair	
3:22:20	Tilted flat	
3:26	122/88	75
3:31	130/86 Asleep	72
3:36	122/86 Awake	66
3:40	132/84	69
3:43	130/82	69
3:46	126/84	66
3:49	132/84 Quiet control period	66
3:50:10	Patient tilted erect (75° from horizontal)	
3:51	?84/55 (muffled sounds)	66
3:51:30	82/66	72
3:52:15	116/76	78
3:53	112/82	75
3:54	114/78	78
3:54:50	Patient looked blank. Began gradually to sink to floor with right leg giving away. Patient held on tilting table and table tilted flat.	
3:55:30	126/84	66
	Right forearm movement at elbow somewhat weaker. Right hand grasp weaker. Can move right leg and foot but power weaker. No Babinski.	
3:58	122/86	72
	Rapidly recovering use of right extremities. Moves right hand, arm, leg and foot easily. Against resistance movement here weaker but coming back strongly. No Babinski.	
4:01:30	132/86	69
4:06:30	126/92	66
	Patient says his right extremities are now normal and in demonstration moves them about in all directions quite freely. Objectively there is slight weakness in right hand grasp and in movement of the right knee. Though slight these changes are definite.	
4:15:30	130/84	66
4:18:18	Tilted erect (90° from horizontal)	
4:19	106/86(?) Muffled sounds	72
	Patient sat down in wheel chair immediately after last blood pressure reading.	
4:21:30	130/90 (seated)	66

An electrocardiographic record of the change produced by pressure over the carotid sinus was taken with the help of Dr. Caroline B. Thomas. With the patient sitting in a wheel chair with head back, pressure was made over the right carotid sinus for 15 seconds. As soon as the pressure was applied the patient began to breathe rapidly and very deeply, the pulse was slowed and became notably much smaller in volume. The patient had been told to inform us if he felt weak or paralyzed. He made an unintelligible sound just at the end of the period of pressure. Afterward he seemed a little confused and perhaps aphasic for a short time and then was able to say that he had felt very dizzy and weak and that he noticed a sensation of pins and needles in his left hand and arm and a little blurring of his vision. The electrocardiogram showed one dropped beat immediately after pressure was begun; then normal sinus rhythm was resumed. The heart rate before pressure was made was 86. The P-P interval of the cycle in which there was no ventricular response corresponded to a rate of 39 per minute. The ventricular pause lasted $2\frac{1}{2}$ seconds. Thereafter the ventricle beat at a rate of 60, gradually increasing to 65 at the end of the period of pressure. Because the cerebral response was so marked on the less affected of the two sides it was decided that it might be dangerous to try pressure over the left carotid artery.

From the foregoing observations we concluded that the patient suffered from arteriosclerosis which was particularly marked in the cerebral artery supplying the area of the brain which controls the right arm and right leg. When he arose from the lying or sitting position to the erect posture, his blood pressure fell and when this fall reached a certain level, ischaemia of the brain occurred. This manifested itself by paralysis in the area corresponding to that supplied by the most sclerosed vessels. Other areas could be similarly affected as shown by the occurrence of weakness in the left arm following temporary occlusion of the right carotid artery.

Treatment devised to prevent a drop in blood pressure low enough to cause symptoms included gradually increasing exercise in the form of walking; massage three times a week; diet to provide a slight loss in weight and to control constipation; abdominal binder to be put on before getting out of bed in the morning; *Ephedrine* 25 mgm. four

times a day; and belladonna three times a day in increasing doses to tolerance. His attacks became much less frequent and less severe and he was sent home to return later for check up.

Interval note: November 17, 1938. The patient after leaving the hospital, went home to his country place and followed the prescribed routine carefully. He took short walks twice daily. Otherwise he rested. He had no further trouble with his legs, but about two weeks after leaving the hospital, on May 21st, he began to have spells of momentary dizziness. He never actually fell, but "things would all go round." About the same time numbness, this time in the right forearm, returned; not necessarily coincident with the dizziness. Attacks varied from 0–2–3 per day. A new symptom appeared—viz. spells of blurring vision in the left eye lasting 30 seconds to a minute. All of these symptoms were most apt to occur in the morning shortly after the patient rose from bed and on several occasions they were brought on merely by his getting up to the sitting position on the side of the bed. For this reason, in addition to the other therapeutic methods, *Benzidrine* 5 mgm. was prescribed, to be taken 15 minutes before arising from bed in the morning. On this treatment the patient was almost free of attacks and those which occurred over a period of 3 months all were mild and permitted him ample time to seek safety in a chair.

During two months, from the middle of November to the middle of January 1939, the patient experienced no attacks but in January a weakness and clumsiness in the right leg developed which gradually disappeared in the course of several days. He has taken *Ephedrine* several times a day and *Benzidrine* the first thing in the morning 15 minutes before getting out of bed. Later this was replaced by *Paredrine sulphate*[1] 5 mgm. and this drug was taken again during the day if he experienced any warning symptoms. Both *Benzidrine* and *Paredrine* seemed to affect adversely the appetite and to cause gaseous abdominal distention and slight constipation. These effects were somewhat less noticeable when *Paredrine* was being taken.

July 5, 1939. Telephone call: The patient reports that he is doing nicely and asks for more *Paredrine* tablets.

[1] Kindly supplied by Smith, French and Kline.

DISCUSSION

A 65 year old man has had innumerable attacks of transient paralysis of the right arm and leg and occasional ones of blurring of the vision of the left eye. These symptoms were reproduced by raising the patient on a tilting table from flat to 75° erect posture, at which time his blood pressure fell momentarily from 130/88 to 82/55 mm. Hg or even lower. The paralysis passed off in 5 or 10 minutes with absolutely no residual.

It is our belief that this apoplexy is caused by a fleeting localized cerebral ischaemia which occurs in the course of a drop of blood pressure from postural hypotension. The degree of narrowing of the lumen from arteriosclerosis of the various cerebral vessels determines the point at which the ischaemia first produces symptoms. So sudden is the paralysis in the leg that the patient falls to the ground if he is not in close reach of a chair.

Stimulation of a hypersensitive carotid sinus may cause a sudden lowering of the blood pressure but one is tempted to suggest that in this patient the postural hypotension is associated with an insensitive reflex pressor mechanism rather than with a hypersensitive reflex depressor mechanism.

The occurrence of transient dimness of vision in one eye vaguely suggested migraine and Mitchell Clarke's (11) report of transient paralysis associated with migraine in members of three generations of one family was recalled. However, there were no other symptoms of migraine and this diagnosis was discarded. Thomas, in his article on apoplexy notes that "Total blindness of one eye due to optic atrophy, secondary to occlusion of the ophthalmic branch of the internal carotid artery, is a symptom of thrombosis of this vessel. The blind eye is on the side of the lesion, and not of the paralysis." Woods (12) reports that arteriosclerosis of the central retinal artery is a common finding. The calcified bodies noted in the x-ray of the region of the internal carotid artery strongly suggest advanced sclerosis of this vessel.

Cases generally similar to this one have been described frequently since the days of Marshall Hall, Todd, Stokes and Abercrombie. Heretofore postural hypotension has not been shown to be associated with attacks of transient paralysis nor with transient dimness of

vision in one eye.[2] The physiological explanation now seems complete and has served in this case as a basis for treatment, with gratifying results.

SUMMARY

A case of recurring transient paralysis of the right arm and leg is reported. The attacks occurred when the patient was upright, and frequently soon after arising from a sitting or lying position. He was found to suffer from a moderate form of postural hypotension which, in conjunction with cerebral arteriosclerosis, offered an explanation for the mechanism of the attacks. When elevated on a mechanical tilting table the systolic blood pressure fell below 90 mm. of mercury and temporary paralysis of the right leg occurred. Most of the previously reported cases of recurrent transient paralysis of brief duration probably belong in the same group.

Momentary clouding of the vision in one eye occurred in some of the attacks and probably resulted from temporarily inadequate blood flow through the ophthalmic branch of the internal carotid artery or the central retinal artery.

Treatment designed to prevent excessive drops in blood pressure has greatly diminished the number and severity of the attacks.

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[2] While this paper was in press an article "Intermittent occlusion of the central retinal artery" by T. D. Saunders (Am. J. Ophth. 1939 (Aug.) 22: 861–869) reported a patient with arteriosclerosis in whom strenuous exercise precipitated demonstrable temporary occlusion of the central retinal artery. Clinical tests seemed to show that the occlusion occurred when the blood pressure rose from the usual 140/90 to 180/100. The author hypothecates spasm in a mildly sclerotic central retinal artery precipitated by elevation in blood pressure and refers to several similar cases in the literature.

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A NOTE ON THE REACTIONS OF THE MOUSE UTERUS TO OVARIECTOMY IN THE PRESENCE OF THE X ZONE

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The extraction of androgens from the adrenal cortex (Reichstein '36 and others) calls for an evaluation of the nature and extent of the andromimetic activity of the adrenal under physiological conditions. The hypertrophy of the adrenal X zone following castration (Howard '27) and the association of a stimulation of seminal vesicle epithelium with the presence of well developed X zone in castrates (Howard '37a, '39a) suggest that any physiological andromimetic activity of the adrenal is probably exerted by the X zone to a greater degree than by the permanent cortex. The vesicle stimulation can be shown to disappear after adrenalectomy of castrated mice under some conditions (Howard '39b).[1] Since the X zone in mice develops to a much greater extent in females than in intact males, it is of interest to know whether it exerts any appreciable antagonistic effect on the female genital tract. Previously we have failed to obtain evidence of such antagonism in studies of normal reproductive activity (Howard '37b). It seemed possible, however, that in the absence of the ovary one might detect some influence of the X zone in accelerating the castration atrophy of the uterus. The possible occurrence of such a reaction was indicated by an incidental observation of Parkes and Brambell

[1] Although these findings suggest that the adrenal may be capable of secreting sufficient andromimetic hormone to be responsible for the anomalous maintenance of columnar epithelium in the vesicles of young castrated mice, nevertheless to what extent and in what way this andromimetic effect is related to the processes involved in the life-maintaining action of the adrenal is not clear at present. More evidence is necessary before one can decide whether the X zone actually does secrete physiologically appreciable amounts of andromimetic hormone.

('27) (see also Parkes '29) that the uterus of the young mouse underwent a most extraordinary degree of involution following ovariectomy, an involution involving dedifferentiation of epithelium and muscle.

It was noted by Wiesner ('34) that this uterine dedifferentiation in the young ovariectomized mouse was not in harmony with his own observations that in the rat differentiation of the uterus up to its prepuberal condition was not modified by removal of the ovaries at birth. This apparent contrast between the mouse and rat thus appeared to be an interesting inverse correlation of the condition in the males of the two species; where, after prepuberal castration, the seminal vesicle epithelium is maintained in a columnar state in the mouse, but is reduced to a cuboidal state in the rat.

Accordingly we have made observations on the reactions of the mouse uterus to ovariectomy at three weeks of age when the X zone is in the process of enlarging, and in full grown mice which, having previously borne litters, were without primary X zone in the adrenal. These two groups of mice were then compared with two similar groups of rats ovariectomized at corresponding periods, namely at weights of 50 grams and 200–240 grams, the latter group having borne litters. All animals were killed 60 days after ovariectomy and their tissues prepared for microscopical study.

It was found, contrary to the observations of Parkes and Brambell, that there had occurred no major qualitative dedifferentiation in the uteri of the prepuberally ovariectomized mice (fig. 1). Comparison with the normal uterus at 21 days (fig. 2) shows that removal of the ovaries at this age was followed by some decrease in size, but no appreciable qualitative histological effect on the uterus. Furthermore there existed no great difference between the X zone-bearing mice and the older mice without primary X zone (fig. 3) nor between the mice and the rats (figs. 5 and 6), in which a definitive X zone is not ordinarily differentiated (Howard '38) and where the homologous adrenal phase persists for a much shorter period, at a younger stage than is included in the present experiments. The uteri of the younger animals were smaller than those of the mature animals which had borne litters, and contained less loose connective tissue, but the typical layers of the uterus had not lost their identity. The lining was composed of the basal epithelium characteristic of the resting uterus, namely a single

layer of nuclei with very little cytoplasm, and was of essentially the same character in the two groups. The differences between the young and mature uteri appeared to be no greater in the mouse than in the rat. The uteri were certainly not reduced to the simple tube structure lined with cornified epithelium, which was pictured by Parkes and Brambell. However, examination of mice ureters revealed a structure (fig. 4) similar to that pictured by these authors as the uterus of a prepuberally ovariectomized mouse (loc. cit., Pl. X, fig. 7). On gross examination, the ureter and uterus are somewhat similar in size and appearance in these young ovariectomized animals, but microscopically there is a difference.

The failure of the X zone to exert an appreciable antagonistic action on the uterus need not be interpreted as evidence against the hypothesis that it has some slight andromimetic activity, since it has been shown by Korenchevsky and Dennison ('36) that androgens actually exert some stimulation of the uterus in castrated rats. However the production of substances stimulating male secondary sex characters cannot normally be a very important aspect of X zone function. Insofar as this may occur it is probably incidental to some quantitatively more important effect of the X zone. The evidence suggestive of actual stimulation of male characters by the X zone in the mouse (Howard '37a, '39a and '39b) and by an analogous though much more brief phase in the maturation of the adrenal of the rat (Howard '37a and '38 and Burrill and Greene '39) shows that ordinarily this effect is at best relatively minor. The observations are of significance in that they do furnish evidence of some relationship between the normal adrenal cortex and certain reactions of the male reproductive system which may assist us in understanding the effects associated with certain kinds of adrenal neoplasms or hyperfunctioning states.

It is worthy of emphasis that there is no evidence that as far as the maintenance of the uterus is concerned, the mouse is different from the rat, in which it has been shown by Wiesner ('34) that differentiation and maintenance of the prepuberal uterus is not dependent on hormones secreted by the ovary. Thus the mouse need not be considered an exception to the rule formulated by Danchakoff ('37) that, in a homogenic sex, sexual histogenesis up to a certain point is not dependent on hormones secreted by the gonad.

SUMMARY

There is no marked qualitative difference in the degree of uterine involution after ovariectomy in mice with or without adrenal X zone, and no evident difference between mice and rats with respect to this uterine reaction. Thus the association between the presence of the X zone and a stimulation of certain male characters has not been found to be supplemented by any suppression of female differentiations.

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PLATE

PLATE I

Explanation of figures

FIG. 1. Uterus of mouse ovariectomized at 21 days of age, examined after an interval of 60 days. In comparison with the normal uterus (fig. 2) there has been some reduction in size but no dedifferentiation. This animal had a well developed primary X zone. × 100.

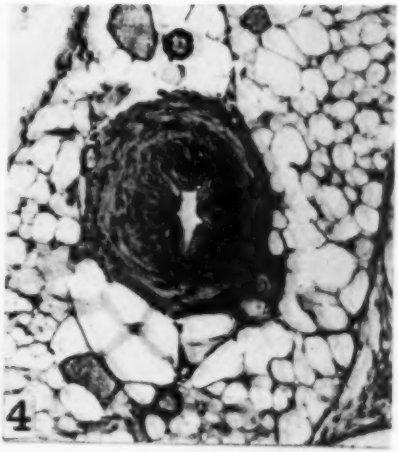
FIG. 2. Uterus of normal mouse at 21 days of age. × 100.

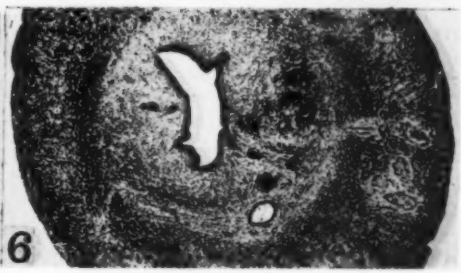
FIG. 3. Uterus of an adult mouse ovariectomized after a pregnancy and examined after an interval of 60 days. No X zone was present in the adrenal. The uterus is larger than that of the immature mouse shown in fig. 1, and contains more loose connective tissue but there is no major difference in histological structure. × 50.

FIG. 4. The ureter of a mouse ovariectomized at 21 days of age. × 200.

FIG. 5. The uterus of a rat, 60 days after ovariectomy at 50 grams body weight. Note general similarity to uterus of young mouse. × 100.

FIG. 6. The uterus of a rat which had borne a litter, and was ovariectomized at 200 grams body weight. Note that the differences between the young and mature mice uteri are not appreciably greater than between the young and mature rat uteri. × 50.





BOOK REVIEWS

(The reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of this Journal.)

Clinical Biochemistry. By ABRAHAM CANTAROW AND MAX TRUMPER. 2nd ed. revised. 666 pp. $6.00. *W. B. Saunders Company, Philadelphia, 1939.*

The authors consider that the new title expresses better than the old, "the broad scope of application of biochemical observations in modern medicine." In the strict sense of the term this volume is not chemistry at all, inasmuch as nowhere in the text is there given a chemical structure or a discussion of the chemical properties of the compounds mentioned. It is, rather, a compilation of facts and theories derived from observations made with the use of chemical tools. In addition to chapters on general topics, such as protein metabolism, there are chapters in which are discussed the pathological metabolism in such diseases as diabetes and nephrosis, and of such functions as those of the liver and kidneys. The chapter on carbohydrate metabolism is outstanding; the chapter on acid-base balance is weak.

This book fills exceedingly well a real need in the teaching of elementary clinical medicine. It is the sort of book for which the student, cramming for an examination, or the instructor, preparing a lecture, is devoutly thankful. The material is excellently organized, well written, lucidly presented. The didactic method used is at the same time a source of both strength and weakness. It is strong because it helps the student to find his way in a maze of details; it is weak because the argument is neither sufficiently fundamental nor sufficiently well bolstered with bibliography to satisfy the inquiring mind. Like most texts on this subject, in which the approach is primarily clinical, this one fails to give the reader an adequate sense of the mobile, dynamic chemical equilibria which determine the course of events in any given circumstances.

M. V. B.

Life and Letters of Dr. William Beaumont. By JESSE S. MYER. With an Introduction by SIR WILLIAM OSLER. New print, entirely reset. xxxi + 327 pp. Illus. $5.00. *The C. V. Mosby Company, St. Louis, 1939.*

All who are familiar with the original edition of this book, published in 1912, will welcome this reprint. It is the only extensive monograph which has ever been written about William Beaumont, the American army surgeon, who is remembered today for his experiments on the gastric juice in the case of Alexis St. Martin. The author has included reproductions and transcriptions of important documents and letters which illustrate Beaumont's life and activities. The book is especially

important because it has made sources available which were otherwise difficult of access. This reprint contains all of the original edition, supplemented by four hitherto unpublished letters of Alexis St. Martin, a modern appreciation of Beaumont's work, and two new illustrations.

G. M.

Failure of the Circulation. By TINSLEY RANDOLPH HARRISON. 2nd. Ed. 502 pp. $4.50. *Williams & Wilkins Company, Baltimore, 1939.*

The reviewer welcomes the opportunity to say a few words in praise of this book which is devoted, in the main, to a study of the causes underlying the signs and symptoms of congestive heart failure. In attempting to prove his case for the "backward failure" theory, the author supports his arguments with the results of many clinical experiments, carried out by himself or under his supervision. This array of clinical data is impressive as well as stimulating. The second edition contains a fuller account of the signs and symptoms produced by impairment of the coronary circulation, and the results of recent experimental work in the field of circulatory failure. One notes, with relief, that the terms "hypokinetic syndrome" and "dyskinetic syndrome" have been replaced by "forward failure" and "backward failure" respectively. Anyone attempting to understand the mechanism of heart failure will be well repaid for a careful study of this book.

R. F.

Analysis of Parergasia. By GLADYS C. TERRY AND THOMAS A. C. RENNIE. 202 pages. $4.00. *Nervous and Mental Disease Publishing Company, New York, 1938.*

This is an important contribution to the study of that group of sweeping personality disorders which is more commonly and less fittingly known as dementia praecox. It is dedicated to, introduced by, and representative of Adolf Meyer, whose classical formulation in 1906 gave new and vigorous direction to the investigation of the parergasia problem. The material consists of 77 cases studied at the Henry Phipps Psychiatric Clinic and representing "a widely diverse series of reactions, all easily brought together under the general heading of content disturbances." The aim is "to show the contrasts as well as the similarities of reaction, and conscientiously to search all the available data for its constitutional, psychogenic, organogenic and exogenic components." It is to this search, conscientious and painstaking indeed, that the word "Analysis" refers in the title.

The subject matter is well organized. A key to the 77 individually coded and charted histories attests the breadth of the enterprise. A discussion of the variety and range of clinical reaction patterns, with brief and well-recorded illustrations, demonstrates clearly the bankruptcy of the idea that one deals with a narrowly circumscribed disease entity, and at the same time offers a review and a tentative grouping of the different behavior constellations (e.g. aggressive, conversion, passivity, deliroid, affective, and defeatist reactions). The principal value of the

work lies in the exquisitely comprehensive account of the patients' life histories, with an unbiased, not prejudicially selected inclusion of all essential data and, skilfully avoiding statistical or merely descriptive looseness, a determination to see and show how things fit together. A chapter on "Outcome" leads the authors to conclude that "prognosis can be viewed with real optimism; nearly half of our patients are managing to adjust to life outside a hospital." Since a statement of prognosis "would best be reserved to a search for workable assets and potentialities," these assets are given special attention in a separate section.

The authors draw on actual observations and events and their meanings and interrelationships. At no time do they succumb to the habit, still to be found among some psychiatrists, of substituting fancies for facts. The material shows definitely that dynamics can be studied from that which is there; then we have the dynamics of the behavior of patients and not the dynamics of the behavior of uncritical theorists. The material shows further that a study of the dynamics is of paramount significance and cannot be dispensed with; the recent surge of shock therapies has tended to obscure that need to some extent.

The richness, objectiveness and inherent honesty of the presentation and the clearness of style and arrangement recommend the monograph not only to psychiatrists but to all physicians, who will find there, besides an "analysis of parergasia," a wealth of information about unwholesomely functioning human beings.

L. K.

Jacob Henle: on Miasmata and Contagia. Translated by GEORGE ROSEN. 77 pp. $1.00. *The Johns Hopkins Press, Baltimore, 1938.*

Those interested in the progress of medical science during the 19th century owe a debt of gratitude to Dr. Rosen for making available in English this valuable contribution. It is a milepost in the transition of thought about the cause of disease written by Henle in 1840, when he was but 31 years of age. It shows a remarkable grasp of current knowledge of contagion. Step by step he marshals a mass of conflicting testimony and by clear, inductive reasoning infers that "miasma" must contain the contagious agent, that this agent must be living and capable of reproduction, and that in all probability it belongs to the world of microscopic plants which, it was then being realized, were widely distributed in nature. With the mind of a true scientist he recognized the limitations of his evidence and admitted that he could only advance an hypothesis. His personality and ideas, nevertheless, exerted a real influence upon one of his students, Robert Koch, who, thirty years later, brought convincing proof that Henle's theory was correct. Henle thus belongs to that small group of brilliant students who, through sheer force of intellect, anticipated the discovery of the microscopic forms of life which are the cause of disease. This book will be a valuable addition to the library of those who are interested in the development of knowledge of infection.

K. F. M.

BOOKS RECEIVED FOR REVIEW

Surgical Treatment of Hand and Forearm Infections. By A. C. J. BRICKEL. 300 pp. Illus. $7.50. C. V. Mosby Company, St. Louis, 1939.

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